

NEPHROTOXICITY OF IONIC AND NON-IONIC CONTRAST MEDIA IN EXPERIMENTAL AND CLINICAL NEPHROANGIOGRAPHY

With special reference to ionic diatrizoate and
metrizoate and non-ionic iohexol

Carl Törnquist



Malmö 1985

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With special reference to ionic diatrizoate and
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av

Carl Törnquist
leg läk, Gbg

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska
fakulteten vid Universitetet i Lund för
avläggande av medicine doktorsexamen kommer
att offentligen försvaras i universitets-
klinikernas aula, Allmänna sjukhuset i Malmö,
fredagen den 8 mars 1985, kl 09.15.

Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION
Department of Diagnostic Radiology Allmänna sjukhuset S-214 01 Malmö Sweden	Date of issue 1985-03-08
Author(s) Carl Törnquist	CODEN: LUMEDW/MEXM-1001/1-116/1985
	Sponsoring organization

Title and subtitle

Nephrotoxicity of ionic and non-ionic contrast media in experimental and clinical nephroangiography. With special reference to ionic diatrizoate and metrizoate and non-ionic iohexol.

Abstract

Intravascular administration of the commonly used ionic ratio 1.5 contrast media (e.g. diatrizoate and metrizoate) means a risk of contrast medium-induced acute renal failure. Thus, there is a need for contrast media with lower nephrotoxicity. The pathogenesis of this renal failure is poorly understood. This was the background for the present investigations demonstrating that:

Selective renal artery injections of the second generation of ratio 3.0 contrast media (non-ionic iopamidol, iohexol and C29 and ionic ioxaglate) affected glomerular permeability (albuminuria) less than diatrizoate and non-ionic metrizamide in dogs.

Selective renal artery injections of large doses of diatrizoate in dogs produced irregular nephrograms, a marked decrease in renal blood flow (electromagnetic flow meter) and a decrease in glomerular filtration rate (creatinine clearance) and an abnormally low osmotic diuresis, whereas iodine-equivalent doses of iohexol and metrizamide produced homogeneous nephrograms and no marked effects on the other parameters.

Selective renal artery injections of large single doses of metrizoate in dogs also produced irregular nephrograms, whereas large total doses, when injected as several small single doses, produced homogeneous nephrograms. The irregular nephrograms were associated with a transient thrombus formation in afferent arterioles and glomerular capillary tufts as demonstrated by light microscopy and accumulation of Cr-51-labeled platelets and I-125-labeled fibrinogen in the kidneys.

In clinical nephroangiography metrizoate produced a transient increase in glomerular permeability and a transient decrease in glomerular filtration rate (serum creatinine and Cr-51-EDTA clearance), whereas iohexol did not affect these parameters.

It was concluded that the nephrotoxicity of the second generation of ratio 3.0 contrast media is less than that of ratio 1.5 media. The future use of these ratio 3.0 contrast media may imply a reduced risk of contrast medium-induced acute renal failure.

Key words

Contrast media, Nephroangiography, Renal angiography, Toxicity, Adverse reactions, Albuminuria, Renal blood flow, Glomerular filtration rate, Diuresis, Nephrograms.

Classification system and/or index terms (if any)

Supplementary bibliographical information

Language
English

ISSN and key title

ISBN

Recipient's notes

Number of pages

116

Price

Security classification

Distribution by (name and address)

Carl Törnquist, M.D., Department of Diagnostic Radiology, Allmänna sjukhuset, S-214 01 MALMÖ, Sweden

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Date 1984 11 22

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ACKNOWLEDGEMENTS

The present investigation was designed and performed at the Departments of Diagnostic Radiology (Head: Professor Tord Olin) and Experimental Research (Head: Professor S.-E. Bergentz), Allmänna Sjukhuset, Malmö, University of Lund, Sweden and the Department of Pathology (Head: Professor O.H. Iverssen), Rikshospitalet, Oslo, Norway.

I wish to express my thanks to:

Professor Tord Olin for encouraging support, constructive discussions and criticism.

Docent Torsten Almén, my teacher and friend, for professional guidance and never-ceasing patience.

Docent Stig Holtås and Professor Klaes Golman for invaluable guidance and encouraging support.

Docent Bertil Nosslin and Docent Ulf Nyman for constructive discussions and criticism.

Mrs. Britt-Marie Lilja, Mrs. Anita Burnett, Mrs. Gail Åkerman, Mrs. Christina Lindqvist and Mr. Georg Hansson for excellent technical assistance.

Mrs. Barbro Falkmer and Mrs. Wivi-Maj Mirén for excellent secretarial help.

Dr. Curt G. Carlbom for revising the English text.

Mr. Rune Olsson and Mr. Peter Osberg for phototechnical assistance.

Nyegaard & Co., Oslo, Bracco, Milan, and Laboratoire Guerbet, Aulnay-sous-Bois, for supplying contrast media.

The investigation was supported by grants from: The Swedish Medical Research Council, projects No. 3483 and B85-17X-00759-20C and the Faculty of Medicine, University of Lund.

To my Mother and Father

and Nina, Karin, Carl, Jocke, AKKA and Lisen

This thesis is based on the following papers:

- I. TÖRNQUIST C., ALMÉN T., GOLMAN K., and HOLTÅS S.:
PROTEINURIA FOLLOWING NEPHROANGIOGRAPHY VII. Comparison
between ionic monomeric, monoacidic dimeric and non-
ionic contrast media in the dog.
Acta Radiol. Suppl. 362 (1980), 49.
- II. TÖRNQUIST C., ALMÉN T., GOLMAN K., and HOLTÅS S.:
RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH DIA-
TRIZOATE. Effects of saline, mannitol, and diatrizoate
on renal blood flow, glomerular permeability and fil-
tration rate and diuresis in dogs.
Acta Radiol. Diagnosis. 25 (1984), 343.
- III. ALMÉN T., BERGENTZ S.-E., TÖRNQUIST C., and ÖYSTESE B.:
IRREGULAR NEPHROGRAMS AND ACCUMULATION OF PLATELETS IN
THE KIDNEY FOLLOWING SELECTIVE NEPHROANGIOGRAPHY IN
DOGS.
Accepted for publication in Acta Radiol. Diagnosis.
- IV. TÖRNQUIST C., ALMÉN T., GOLMAN K., and HOLTÅS S.:
RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH METRIZ-
AMIDE AND IOHEXOL. Effects on renal blood flow, glomer-
ular permeability and filtration rate and diuresis in
dogs.
Accepted for publication in Acta Radiol. Diagnosis.
- V. TÖRNQUIST C., and HOLTÅS S.:
RENAL ANGIOGRAPHY WITH IOHEXOL AND METRIZOATE.
Radiology 150 (1984), 331.

References to these papers will be made by the Roman numerals
I-V.

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CONTRAST MEDIUM-INDUCED ACUTE RENAL FAILURE

Iodinated water-soluble contrast media for intravascular use have been employed in diagnostic radiology since the 1920s. In everyday practice such media were not used in patients with impaired renal function before the 1960s. The reason for this was the experience that urography yielded low contrast medium concentration in the urinary tract and therefore insufficient diagnostic information but there was also a fear of contrast medium-induced further deterioration of renal function.

The nowadays commonly used water-soluble ionic triiodinated contrast media (i.e., diatrizoate, iodamide, iothalamate, ioxithalamate, and metrizoate) were successively introduced from the middle of the 1950s and replaced previously used media because of a lower toxicity (9, 29, 55, 96). In the early 1960s it was demonstrated that the urinary tract could be visualized also in patients with renal failure when urography was performed with large doses of these media; moreover, this procedure did not seem to produce any further deterioration of renal function (83). This meant a major diagnostic improvement in the evaluation of urinary tract obstruction in those patients and retrograde pyelography could be avoided in many instances. Since then, there has been an increasing use of large doses of these media for urography, angiography, and computed tomography. The nephrotoxicity of these media was generally considered low or almost negligible for many years (1, 18, 22, 25, 31, 48), although there were reports of renal complications (21, 30, 72).

However, in the last decade, an increasing number of cases of acute renal failure following intravascular administration of the commonly used ionic contrast media have been reported (65). In the years 1980-1983 more than 200 cases have been reported, but they probably represent only a fraction of the cases that actually occurred.

Reviews on incidence, risk factors, clinical course, and possible pathogenesis of contrast medium-induced acute renal failure have been given by BYRD & SHERMAN (15), MUDGE (65), HARKONEN & KJELLSTRAND (33), MUDGE et coll. (66), and BERKSETH & KJELLSTRAND (10). These subjects will briefly be commented on.

INCIDENCE AND RISK FACTORS. The true incidence of contrast medium-induced acute renal failure is not known. There is an extreme variation in incidence between different reports and this is probably partly related to the designs of the investigations, i.e., prospective or retrospective, inclusion criteria and exclusion criteria for studied populations. Moreover, various diagnostic criteria for contrast medium-induced acute renal failure have been used; most authors have arbitrarily defined renal failure as an increase in serum creatinine of at least 1 mg/dl ($\approx 90 \mu\text{mol/l}$) (66). In many cases of transient renal failure the diagnosis will be overlooked if biochemical parameters, such as serum creatinine, are not monitored.

The reported incidence of contrast medium-induced acute renal failure varies from zero or a few per cent to more than 90 per cent. The low incidence has been reported from studies of hospitalized patients with various diseases referred for urography (25, 31) and angiography (22, 48), whereas the high incidence was found in studies of diabetic patients with preexisting renal insufficiency referred for urography (32, 84) and angiography (99). The incidence of contrast medium-induced acute renal failure following intravenous administration in non-hospitalized patients without renal failure is probably low but unknown.

The variation in incidence is related to various risk factors of which preexisting renal insufficiency and diabetes mellitus associated with renal insufficiency are the most important. There are opposing views as regards the significance of some other reported risk factors (Table 1).

Table 1. Some reported risk factors of contrast medium-induced acute renal failure and references

preexisting renal insufficiency	(10, 15, 71, 95)
diabetes mellitus, especially associated with renal insufficiency	(10, 32, 84, 99)
multiple myeloma	(13, 62)
transplanted kidneys	(34, 53)
dehydration	(10, 21, 72)
hypertension	(15, 95)
advanced age	(15, 46)
dosage of contrast medium	(15, 59, 71)
short interval between contrast medium procedures	(46, 60)

The great clinical importance of contrast medium-induced acute renal failure may be revealed by the following: In a survey of 620 cases of acute renal failure of various etiologies referred to a nephrologic clinic, it was found that 5 per cent were caused by intravascular administration of water-soluble contrast media, and in this group the mortality was 36 per cent (7). In a recent prospective study of 2216 hospitalized patients, episodes of acute renal failure of various etiologies were observed in 4.9 per cent and of these 12 per cent were caused by water-soluble contrast media (40).

CLINICAL COURSE. The clinical course of contrast medium-induced acute renal failure may range in severity from a transient decrease in glomerular filtration rate, only detectable by biochemical parameters such as serum creatinine, to anuria requiring hemodialysis, and eventually death. In a review of 284 cases of contrast medium-induced acute renal failure,

MUDGE (65) reported a benign course, i.e., return of renal function to normal, in 69 per cent, whereas 12 per cent recovered but with a partial loss of renal function. Death due to uremia or renal failure requiring chronic dialysis or kidney transplantation occurred in 19 per cent of these 284 cases.

Various associated symptoms and findings to contrast medium-induced acute renal failure have been reported. For instance, the urine production may vary from normal to oliguria and anuria (65). Proteinuria (8, 66, 93) and hematuria (30) may be associated findings. Renal biopsies have shown "acute tubular necrosis" (46, 95) or "proliferative glomerulonephritis" (12). A "persistent nephrogram", lasting for hours up to several days, may be demonstrated (8, 20, 71).

PATHOGENESIS. In most toxic nephropathies, including contrast medium-induced acute renal failure, the pathogenesis is incompletely known. A large number of contrast medium effects, which may affect the kidney and its function, have been observed or measured in vitro or in vivo in animals and humans. Based on these a number of hypothetical pathogenetic mechanisms have been proposed. A survey of these hypothetical mechanisms and a number of observed or measured effects of contrast media that are compatible with the hypothetical mechanisms are given in Table 2.

A schematic presentation of hypothetical mechanisms and observed or measured effects as in Table 2 is often used in reviews of contrast medium-induced acute renal failure (10, 15, 33) and may be justified to achieve surveyability. However, it may be an incorrect simplification because there may exist causal relations between the hypothetical mechanisms. Furthermore, several of the observed or measured effects are compatible with different hypothetical mechanisms. This view may be elucidated by the following:

Contrast media may produce "hemodynamic disturbances" (Table

2). These may affect tubular cells and their function. Tubular cell damage may mean leakage of proteins ("enzymuria") or cell debris into the tubules, where they may precipitate, and such effects may be included in the hypothetical mechanism "intra-tubular obstruction".

Contrast media may produce an increase in intratubular pressure (43, 66). This may be caused by the osmotic diuresis, which is produced by the filtrated hyperosmolar contrast medium, but it may also be caused by effects producing "intratubular obstruction" (Table 2). Increased intratubular pressure, whatever the cause, may affect glomerular filtration rate by reducing the effective filtration pressure, but it may also affect renal blood flow by capillary compression. On the other hand, reduced glomerular filtration rate may be secondary to a reduction in renal blood flow, meaning a reduced plasma flow.

Table 2 and these examples may give an idea of the complexity of mechanisms that may be involved in contrast medium-induced acute renal failure. The pathogenesis may be multifactorial with different mechanisms and risk factors dominating in different cases of renal failure, an assumption which may be supported by the wide variation in both the clinical course and the symptoms of the individual patient.

Table 2. Various hypothetical mechanisms that may be involved in the pathogenesis of contrast medium-induced acute renal failure are given in capital letters. Under each of these a number of observed or measured effects of contrast media that are compatible with the hypothetical mechanisms are given. References in parentheses (some of these effects have been listed twice as they are compatible with different hypothetical mechanisms). For further discussion see the text

HEMODYNAMIC DISTURBANCES AND ISCHEMIA

reduction in renal blood flow.....	(15, 30, 42)
shift in oxyhemoglobin dissociation curve....	(79)
increased blood viscosity	(6)
erythrocyte alterations.....	(6)
endothelial damage.....	(69)
platelet aggregation.....	(100)
thrombus formation.....	(14, 78)
increased intratubular pressure → capillary compression.....	(43, 66)
reduced glomerular filtration rate.....	(23, 43, 52, 60, 67, 75)

INTRATUBULAR OBSTRUCTION

gel formation of Tamm Horsfall mucoproteins..	(8, 82)
albuminuria (glomerular leakage).....	(35)
increased excretion of uric acid.....	(74)
increased excretion of oxalate.....	(26)
reduced glomerular filtration rate.....	(23, 43, 52, 60, 67, 75)
increased intratubular pressure.....	(43, 66)

TUBULAR CELL DAMAGE

enzymuria.....	(27, 44, 91)
acute tubular necrosis.....	(46, 95)
osmotic nephrosis.....	(61)
medullary necrosis.....	(30)
increased mitotic rate.....	(88)
reduced PAH-clearance.....	(19)
depression of sodium transport.....	(101)

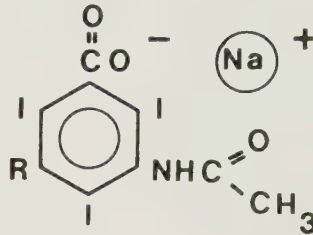
IMMUNOLOGIC MECHANISMS

proliferative glomerulonephritis.....	(12)
antibody formation.....	(45)
rejection-like conditions of transplanted kidneys.....	(34, 53)
complement activation.....	(34)

ASPECTS ON THE CHEMISTRY AND TOXICITY OF MODERN CONTRAST MEDIA

The commonly used water-soluble contrast media (i.e., diatrizoate, iodamide, iothalamate, ioxithalamate, and metrizoate) are all salts of triiodinated benzoic acid. Their principal chemical structure is given in Fig. 1.

Fig. 1. Principal chemical structure of ionic monomeric contrast media.



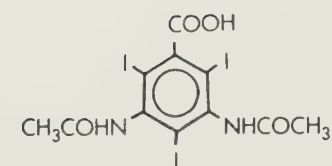
In solution they dissociate into ions, and as they contain one iodinated aromatic ring, they are referred to as ionic monomeric contrast media. The cations are sodium, calcium, magnesium and/or meglumine. They differ as regards the radical R (Fig. 1). The osmolality of their solutions is theoretically determined by the number of particles in the solutions. The radiopacity of their solutions is determined by the number of iodine atoms. The ratio between the number of iodine atoms and the number of particles in an ideal solution of these media is $3/2 = 1.5$ and expresses the radiopacity relative to the osmolality of the contrast medium solution.

The toxicity of contrast media can be attributed to the toxicity of the contrast media molecules and to other components of the solutions, but also to the hyperosmolality of the solutions (3, 89). Ionic ratio 1.5 media are in commonly used concentrations hyperosmolar in the range of five to eight times that of human plasma.

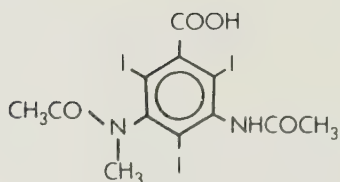
In order to increase the tolerability of contrast media, one

approach is to reduce their osmolality in relation to their iodine content, and this can be achieved by increasing the ratio between the number of iodine atoms and the number of particles in solution. According to this principle, the development of non-ionic ratio 3.0 contrast media was initiated (2) and metrizamide was the first to come into clinical use. The chemical structure of metrizamide is given in Fig. 2. The carboxyl group of metrizoic acid has been exchanged with a radical (glucosamide) that does not dissociate in solution and thereby the ratio will be $3/1 = 3.0$. Theoretically, this medium should have half the osmolality of ratio 1.5 media. However, at high iodine concentrations the measured osmolality of metrizamide is only one third of that of the ionic media, and this is explained by aggregation of metrizamide molecules in solution. Metrizamide has the disadvantages of not tolerating autoclaving and is supplied as a freeze-dried substance, which must be dissolved before use. Partly due to the sterilization procedure, the price of metrizamide greatly exceeds that of ionic monomeric media.

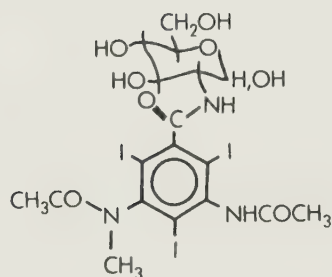
In order to overcome these disadvantages, a second generation of ratio 3.0 contrast media has been developed, e.g., non-ionic iopamidol, iohexol, C29, and ionic ioxaglate (Fig. 2). In these non-ionic media the glucosamide of metrizamide has been exchanged with other hydroxyalkylamide radicals and they also differ as regards the radicals in the 3 and 5 positions. The ionic ioxaglate is a monoacidic dimeric medium (Fig. 2), in which one of the two carboxyl groups of a di-acidic dimer has been exchanged with a non-dissociating radical. In solution such a molecule dissociates into one cation and one anion containing six iodine atoms, i.e., the ratio will be $6/2 = 3.0$. The second generation of ratio 3.0 contrast media tolerate autoclaving, are supplied as sterile solutions and the price has been reduced. Iopamidol, iohexol, and ioxaglate are now in clinical use, whereas C29 was discarded for clinical trials due to the appearance of crystals in the supersaturated solutions.



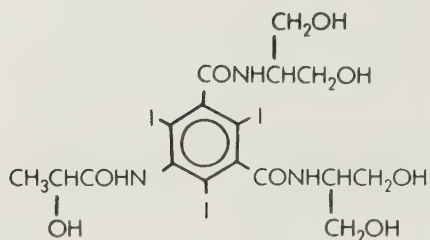
Diatrizoic acid



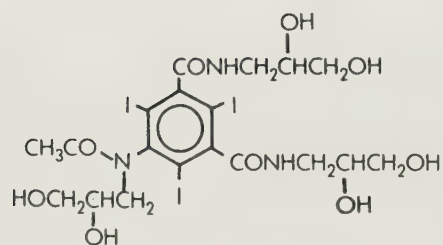
Metrizoic acid



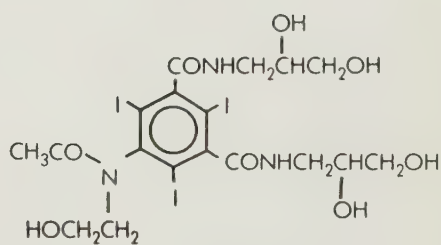
Metrizamide



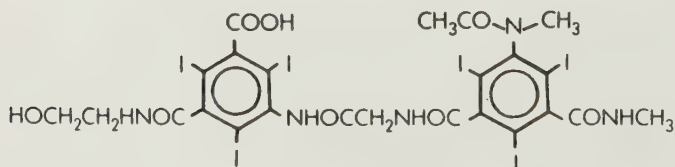
Iopamidol



Iohexol



C29



Ioxaglic acid

Fig. 2. Chemical structures of the contrast media in the present investigations.

Experimental and clinical research have demonstrated that intravascular use of ratio 3.0 contrast media signifies several advantages when compared with the ratio 1.5 media, such as reduced acute intravenous toxicity and in angiographic procedures reduction in pain, reduction in hemodynamic effects, including less endothelial cell damage and less pronounced erythrocyte changes (5, 6, 11, 29, 54). However, the nephrotoxicity of the first non-ionic ratio 3.0 contrast medium, me-trizamide, has been found to be approximately the same as that of the ratio 1.5 media by most investigators (5, 38, 39, 47, 61, 88). There are reports suggesting that the nephrotoxicity of the second generation of ratio 3.0 contrast media is less than that of ratio 1.5 media (44, 56, 57, 68, 73, 81, 90, 94).

From this introduction the following will be advanced:

1. Contrast medium-induced acute renal failure following intravascular administration of water-soluble ratio 1.5 media is a serious complication in clinical radiology. Although the incidence may be low, the problem is of great importance because several millions of patients are exposed to these media every year and many of them belong to risk groups. Moreover, the use of contrast media is increasing (50).
2. The mechanism(s) by which the contrast media and the risk factors produce acute renal failure are poorly understood and the pathogenesis may be multifactorial. Different effects of contrast media may dominate in different cases of contrast medium-induced acute renal failure. This means difficulties in designing adequate studies on nephrotoxicity, and therefore it is suggested that evaluation of nephrotoxicity of contrast media

should reflect several aspects of kidney function.

3. To elucidate the nephrotoxicity of the second generation of ratio 3.0 contrast media, further research is warranted.

AIMS OF THE PRESENT INVESTIGATION

The aims of the present investigation were

1. to further evaluate effects on the kidney of ratio 1.5 contrast media in attempts to find mechanisms that may be involved in contrast medium-induced acute renal failure;
2. to compare effects on the kidney of ratio 1.5 media to those of ratio 3.0 media in attempts to find contrast media with lower nephrotoxicity than that of the ratio 1.5 media.

Holtås (35) used postangiographic albuminuria, analyzed in samples from the bladder, as an indicator of contrast medium effects on the kidney in dogs and humans, and during the course of that project an irregular (non-homogeneous) nephrogram was occasionally observed following selective renal artery injections of diatrizoate in dogs (Fig. 4a, p. 23).

From this background it was decided:

- to compare effects on glomerular permeability, i.e., albuminuria following selective unilateral renal artery injections of four ratio 3.0 contrast media (iopamidol, iohexol, C29, and ioxaglate) and one ratio 1.5 medium (diatrizoate) in dogs by analyzing urine samples from the bladder (I);
- to compare effects on glomerular permeability of diatrizoate, metrizamide, and iohexol following selective unilateral renal artery injections in dogs by analyzing urine samples separately from each ureter and to simultaneously investigate

and compare (II, IV):

- the nephrograms
- renal blood flow in the injected artery
- glomerular filtration rate (separately for each kidney)
- the diuresis (separately from each kidney).

Diatrizoate produced in high frequency an irregular (non-homogeneous) nephrogram. It was postulated that the phenomenon could be caused by irregularly distributed vascular and/or tubular obstructions in the kidney. Therefore it was decided:

- to investigate irregular (non-homogeneous) nephrograms following selective renal artery injections of metrizoate in dogs as regards (III):
- association with intrarenal thrombus formation and;
- dose dependence.

Finally, it was decided:

- to compare effects on glomerular permeability and filtration rate of metrizoate and iohexol when used in clinical nephroangiography (V).

SUMMARIES OF MATERIAL, METHODS, AND RESULTS

The details of material, methods, and results are given in papers I-V.

The chemical structures of the contrast media in the investigations are given in Fig. 2.

Pertinent data on the contrast media and other test solutions used in the investigations are given in Table 3.

Urinary albumin concentrations were determined by immunochemical methods (51, 58) and were expressed per gram of urinary creatinine, thereby relating albumin excretion to glomerular filtration rate.

Serum and urinary creatinine concentrations were determined using the Jaffé reaction.

Statistics. Statistical significances were evaluated with Wilcoxon's test for paired observations and Mann-Whitney's test for unpaired data in papers I and II and IV and V. In paper III Mann-Whitney's test and Fischer's exact probability test for independent samples were used. p-values of 0.05 or less were considered statistically significant. The term significant implies statistical significance.

Abbreviations:	RBF	renal blood flow
	GFR	glomerular filtration rate
	RPA	relative platelet accumulation
	RKW	relative kidney weight
	b.w.	body weight

Table 3. Pertinent data on the contrast media and other test solutions used in the present investigations*

Generic Name	Trade Name	Iodine Content (mg/ml)	Osmolality (mol/kg H ₂ O)	Concentration (mol/l)	Viscosity (mPa x s)	
					20°C	37°C
Diatrizoate	UROGRAFIN 76%	370	2.10	0.97	18.5	8.9
Metrizoate	ISOPAQUE CEREBRAL	280	1.46	0.73	7.1	4.0
Metrizoate	ISOPAQUE CORONAR	370	2.15	0.96	17.3	8.4
Metrizamide	AMIPAQUE	370	0.58	0.97	37.0	16.0
Iopamidol	SOLUTRAST	370	0.80	0.97	18.5	8.6
Iohexol	OMNIPAQUE	300	0.69	0.79	11.6	6.1
Iohexol	OMNIPAQUE	370	0.98	0.97	29.6	13.5
C29	-	370	0.62	0.97	23.0**	10.6**
Ioxaglate	HEXABRIX	370	0.67***	0.49	40.0****	16.5****
Saline	NACL	-	0.28	0.16	1.1	0.75
Mannitol	MANNITOL	-	0.95	0.82	1.8	1.4

* Data as given by the manufacturer

** Estimated by interpolation

*** Estimated by extrapolation

**** Estimated by Nyegaard & Co.

Paper I: PROTEINURIA FOLLOWING NEPHROANGIOGRAPHY. Comparison between ionic monomeric, monoacidic dimeric and non-ionic contrast media in the dog

Material and methods. Forty-three mongrel dogs were anesthetized with pentobarbitone and breathed spontaneously through an endotracheal tube. A transurethral catheter was placed in the bladder. For selective renal artery injection, a catheter was inserted via one of the femoral arteries. In each dog selective unilateral renal artery injection of a contrast medium (0.5 ml/kg b.w.; 370 mg iodine/ml) was performed under fluoroscopy. After an average period of 10 days (3-32 days), the contralateral kidney was selectively injected with another contrast medium at the same dose and concentration under the same conditions.

The dogs were divided into three groups. In each group the changes in the concentration of urinary albumin were recorded following injection of two different contrast media: group I: diatrizoate-iopamidol (10 dogs); group II: diatrizoate-iohexol (24 dogs); and group III: C29-ioxaglate (9 dogs). The order of injection was randomized.

Creatinine and albumin concentrations were determined in a blood sample taken before and in urine samples taken before and 15, 30, and 60 min after each contrast medium injection. The maximum value of postinjection urinary albumin concentrations were used in the statistical evaluation.

Results. There were no significant differences in the concentrations of creatinine and albumin in serum between the samples taken before the first and the second contrast medium injection in the groups. There were no significant differences in the concentration of urinary albumin between the samples taken before the first and the second contrast medium injection in the groups or between preinjection samples for each contrast medium in the groups. Selective renal artery injection of all

contrast media induced significant increases in urinary albumin concentrations (Table 4). Diatrizoate produced significantly more albuminuria than the other contrast media. No significant differences in postinjection albuminuria were found between iopamidol, iohexol, C29, and ioxaglate.

Table 4. Preangiographic and maximum postangiographic concentration of urinary albumin in gram albumin per gram urinary creatinine. Median concentration and range in parentheses

Group	Contrast medium	Concentration of albumin in urine	
		Before angiography	After angiography
I	Diatrizoate	0.033 (0.0080-0.090)	27 (1.22-124)
	Iopamidol	0.024 (0.011-0.084)	1.2 (0.14-71)
II	Diatrizoate	0.034 (0.0060-0.57)	11 (0.20-180)
	Iohexol	0.064 (0.0036-0.96)	2.1 (0.12-18)
III	C29	0.030 (0.012-0.10)	0.67 (0.058-14)
	Ioxaglate	0.015 (0.0064-0.074)	2.5 (0.14-17)

Papers II and IV:

II. RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH DIATRIZOATE. Effects of saline, mannitol, and diatrizoate on renal blood flow, glomerular permeability and filtration rate and diuresis in dogs

IV. RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH METRIZAMIDE AND IOHEXOL. Effects on renal blood flow, glomerular permeability and filtration rate and diuresis in dogs

Material and methods. Thirty-six mongrel dogs were anesthetized with pentobarbitone and fentanyl and connected to a respirator by an endotracheal tube.

After laparotomy a flow probe was applied around the left renal artery for continuous mean volumetric blood flow recording with an electromagnetic flow meter connected to a recorder. For urine flow measurements and urine sampling, a catheter was inserted into each ureter. A catheter was inserted into each femoral artery. The left catheter was used for injecting the test solution into the left renal artery. The tip of the right catheter was placed in the abdominal aorta for pulse and blood pressure recording (to monitor the conditions of the dogs during the experiments). The experimental model is schematically illustrated in Fig. 3.

The test solutions were diatrizoate (8 dogs), metrizamide (9 dogs), iohexol (9 dogs), saline (7 dogs), and mannitol (3 dogs). All contrast media had an iodine content of 370 mg iodine/ml (Table 3).

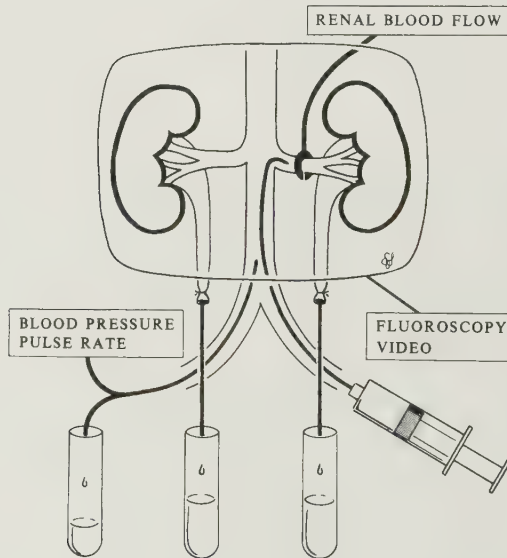


Fig. 3. The experimental model.

Each dog received three selective left renal artery injections of one of the test solutions at 15-min intervals dosed at 1 ml/kg b.w. in each injection. Immediately after each injection the catheter tip was withdrawn to the aorta. No injection was given to the right kidney, which served as a control.

Injections of the contrast medium and the enhancement of the renal parenchyma, with regard to distribution and time (the nephrogram), were monitored by fluoroscopy and recorded on videotape throughout the experiment. The nephrograms were evaluated as homogeneous (Fig. 4b) or irregular (non-homogeneous; Fig. 4a). These irregular nephrograms arose from an initially homogeneous nephrogram and they are therefore referred to as "patchy contrast medium retention" (details of the development of the nephrograms are given in the results).

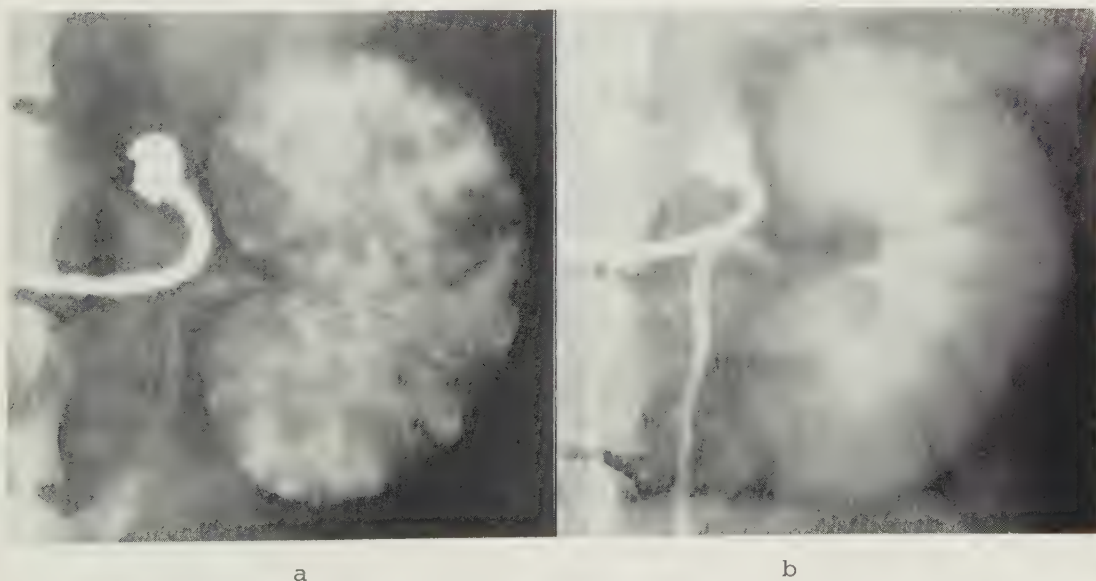


Fig. 4. a) Dog kidney with irregular (non-homogeneous) nephrogram ("patchy contrast medium retention") following selective renal artery injections of diatrizoate. b) Dog kidney with homogeneous nephrogram.

Figure 5 demonstrates the time schedule and the measurements of left renal artery blood flow (RBF) of each experiment. Two dogs in the metrizamide group and one in the iohexol group were excluded from the RBF calculations because of a technical fault in the RBF recorder.

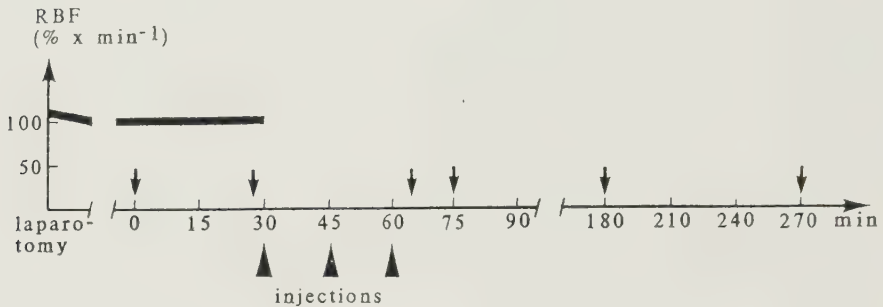


Fig. 5. The time schedule and the measurements of left renal artery blood flow (RBF). RBF was continuously measured, but for statistical calculations selected measurements were made as indicated by small arrows. After applying the flow probe and closing the abdominal incision, the RBF decreased 10 to 20 per cent for 15 to 20 min and then stabilized. Injections of test solution (large arrows) were not given until the RBF had been stable (fluctuation less than $\pm 10\%$) for 30 min. The beginning of this 30-min period was defined as time "0" on the abscissa and the RBF in this 30-min period was in each experiment assigned the value $100\% \times \text{min}^{-1}$. Postinjection RBF was expressed as a percentage of the preinjection RBF and was measured 5, 15, 120 and 210 min (small arrows) after the third injection of test solution. The time scale has been changed after 95 min.

Urine flow was calculated from measurements of urine volumes from each kidney from time "0" (Fig. 5) during every 15-min period up to 90 min and then during every 30-min period up to 270 min. The diuresis was expressed in $\mu\text{l} \times \text{min}^{-1} \times \text{kg b.w.}^{-1}$. In urine samples collected from each kidney before injections (0-30 min, Fig. 5) and after the third injection (60-75 min, Fig. 5), the concentration of creatinine and albumin was determined. An arterial blood sample for creatinine analysis was

drawn before injecting the test solution. Creatinine clearance for each kidney was calculated for the periods 0-30 min and 60-75 min (Fig. 5) according to the formula:

$$Cl = \frac{V \times U}{P \times b.w.}$$

Cl = creatinine clearance ($\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$)

V = urine flow ($\text{ml} \times \text{min}^{-1}$)

U = urinary creatinine ($\mu\text{mol} \times \text{l}^{-1}$)

P = serum creatinine ($\mu\text{mol} \times \text{l}^{-1}$)

b.w. = body weight (kg)

Results. The results are given in Tables 5 and 6.

Renal blood flow (RBF). Following injections of diatrizoate (Table 5, complete diatrizoate group, $n = 8$), the RBF was not significantly reduced when measured 5 and 15 min after the third injection, but 120 and 210 min later the RBF was significantly reduced as compared with the preinjection RBF. Following injections of metrizamide, iohexol, and saline, RBF was not significantly reduced when compared to the preinjection RBF. Postinjection RBF in the diatrizoate group ($n = 8$) did not differ significantly from the other groups on the two first measurement occasions, but was significantly lower on the two last measurement occasions compared with the iohexol and saline groups but did not differ significantly from the RBF in the metrizamide group. Postinjection RBF did not differ significantly between the metrizamide, iohexol, and saline groups.

During the injections of diatrizoate, metrizamide, and iohexol, arterial spasm or occlusions of major renal arteries were not observed. Injections of all contrast media produced an intense

Table 5. Renal blood flow (RBF) in the left renal artery after selective left renal artery injections of the various test solutions, calculated 5, 15, 120, and 210 min after the third injection (corresponding to 65, 75, 180, and 270 min in Fig. 5). Number of dogs in each group = n. Diatrizoate, (n=8) = complete group. Diatrizoate, (n=5) = a subgroup of dogs with patchy contrast medium retention. All values as a percentage of preinjection RBF. Median and range in parentheses

	5 min postinj.	15 min postinj.	120 min postinj.	210 min postinj.
Diatrizoate (n=8)	41 (6-106)	44 (16-114)	61* (22-89)	55* (29-86)
Diatrizoate (n=5)	16*** (6-60)	19*** (16-24)	57* (22-89)	48* (29-86)
Metrizamide (n=7)	83 (56-103)	88 (63-103)	88 (56-120)	67 (52-124)
Iohexol (n=8)	93 (25-133)	96 (25-122)	100 (72-107)	84 (64-100)
Saline (n=7)	96 (80-100)	90 (80-100)	88 (70-120)	84 (54-100)
Mannitol (n=3)	88 (88-113)	88 (80-94)	100 (94-109)	88 (83-113)

* $p < 0.05$; *** $p < 0.01$ compared with saline group

homogeneous radiopacity of the left kidney. A few minutes after the first injection an irregular nephrogram (Fig. 4a) was observed in five of eight diatrizoate-injected dogs. During the subsequent injections of diatrizoate, there was again an intense homogeneous radiopacity and a few minutes later an even more irregular nephrogram was observed in these five dogs (i.e., the size of the "patches" of contrast medium and in some instances the number of "patches" had increased). The irregular nephrogram was observed 120 to 210 min after the last injection in four of these five dogs and for 30 min in the fifth. These five dogs with irregular nephrograms had on

all four measurement occasions a marked decrease in RBF (Table 5; diatrizoate, $n = 5$), which was significantly lower than in the saline group and in the iohexol group (Table 5). When compared to the metrizamide group, the dogs with irregular nephrograms had significantly lower RBF 5 and 15 min postinjection, but at the two last measurements there was no significant difference. Three diatrizoate-injected dogs and all metrizamide- and iohexol-injected dogs showed homogeneous nephrograms (Fig. 4b) and no marked effects on RBF.

Albuminuria. There were no significant differences in preinjection urinary albumin concentrations between the left and right kidneys in the diatrizoate, metrizamide, or saline group or between these groups (Table 6). In the iohexol group the preinjection urinary albumin concentrations for the right kidneys were significantly lower than for the left kidneys. The preinjection urinary albumin concentrations for the left kidneys in the iohexol group did not differ significantly from the preinjection values for the left kidneys in the other three groups.

Injections of all three contrast media increased the urinary albumin concentrations (Table 6), whereas these injections did not affect the albumin concentrations of the non-injected kidneys in any group. Injections of diatrizoate and metrizamide produced significantly higher urinary albumin concentrations than iohexol. Injections of saline did not affect the urinary albumin concentrations.

Macroscopic hematuria was observed in postinjection urine samples from five of eight kidneys injected with diatrizoate, from five of nine kidneys injected with metrizamide, and from one of nine kidneys injected with iohexol. There was no macroscopic hematuria in urine samples from the control kidneys or from saline-injected kidneys.

Creatinine clearance. There were no significant differences in

Table 6. Pre- and postinjection values of albuminuria, creatinine clearance, and diuretics are given for injected (left) and non-injected (right) kidneys of dogs given the various test solutions into their left renal artery. The albuminuria is expressed in g albumin x g creatinine⁻¹, creatinine clearance in ml x min⁻¹ x kg⁻¹, and the diuretics in $\mu\text{l} \times \text{min}^{-1} \times \text{kg}^{-1}$. The sampling periods are illustrated in Fig. 5. Number of dogs in each group = n. Median and range in parentheses

		Albuminuria		Creatinine clearance		Diuresis	
		Preinj. (0-30 min)	Postinj. (60-75 min)	Preinj. (0-30 min)	Postinj. (60-75 min)	Preinj. (0-30 min)	Postinj. (30-270 min)
Diazirizate (n=8)	Injected	0.93 (0.091-3.1)	380*** (16-830)	0.85 (0.25-1.2)	0.28* (0.11-0.92)	2.7 (1.0-4.3)	18* (8.3-41)
	Non-injected	0.37 (0.030-3.4)	0.16 (0.060-0.63)	0.71 (0.29-1.6)	0.85 (0.74-1.6)	2.5 (0.97-3.7)	25 (15-75)
Metrizamide (n=9)	Injected	0.31 (0.13-1.3)	510*** (25-1000)	0.52 (0.31-1.6)	0.68 (0.34-0.94)	3.0 (1.0-5.3)	16* (9.2-27)
	Non-injected	0.36 (0.027-1.8)	0.71 (0.10-1.7)	0.65 (0.34-1.4)	0.89 (0.51-1.4)	3.2 (1.3-6.0)	10 (6.3-13)
Iohexol (n=9)	Injected	0.72 (0.13-3.5)	24** (0.94-76)	0.75 (0.43-1.0)	0.76 (0.19-1.2)	1.9 (1.3-9.3)	17*** (12-30)
	Non-injected	0.46 (0.10-0.53)	0.39 (0.070-4.9)	0.79 (0.55-1.6)	0.94 (0.24-1.4)	1.9 (1.2-12)	10 (7.9-28)
Saline (n=7)	Injected	0.34 (0.15-3.1)	0.43 (0.12-1.5)	0.70 (0.18-0.95)	0.68 (0.24-0.73)	2.2 (1.7-2.8)	2.7 (2.2-3.9)
	Non-injected	0.29 (0.055-0.95)	0.21 (0.12-1.7)	0.64 (0.19-1.1)	0.63 (0.27-1.1)	2.4 (1.5-3.2)	2.7 (2.0-4.2)
Mannitol (n=3)	Injected	0.53 (0.39-1.4)	0.94 (0.33-1.7)	0.96 (0.57-1.1)	1.5 (0.92-1.6)	2.4 (1.5-3.3)	16 (12-18)
	Non-injected	0.35 (0.22-0.39)	0.40 (0.19-1.2)	0.97 (0.77-1.2)	0.94 (0.57-1.3)	1.9 (1.9-3.1)	7.9 (6.7-9.6)

p<0.02; *p<0.01 compared with preinj. values

*p<0.05 compared with preinj. values

*p<0.05; ***p<0.01 compared with non-inj. kidneys

preinjection creatinine clearance between the left and the right kidneys or between the groups (Table 6). Injections of metrizamide, iohexol, and saline did not significantly influence creatinine clearance. Injections of diatrizoate reduced the median value of creatinine clearance to approximately one-third of the preinjection value (Table 6), whereas these injections did not significantly influence creatinine clearance of the non-injected kidneys.

Diuresis. There were no significant differences in preinjection diuresis between the left and the right kidneys or between the groups (Table 6). Injections of all contrast media and mannitol increased the diuresis from both kidneys. Injections of diatrizoate induced a significantly lower diuresis from the injected kidneys as compared to the non-injected ones, whereas injections of metrizamide and iohexol induced a significantly higher diuresis from the injected kidneys compared with the non-injected ones. Injections of mannitol also induced a higher diuresis from the injected kidneys as compared to the non-injected ones in three dogs.

Paper III: IRREGULAR NEPHROGRAMS AND ACCUMULATION OF PLATELETS IN THE KIDNEY FOLLOWING SELECTIVE NEPHROANGIOGRAPHY IN DOGS

Material and methods. Twenty-two mongrel dogs were splenectomized 2-3 weeks prior to nephroangiography. One day before nephroangiography autologous platelets of all dogs were labelled in vitro with Cr-51. In ten dogs allogenic fibrinogen was labelled in vitro with I-125 and was injected intravenously 2-5 days prior to nephroangiography.

The dogs were anesthetized with pentobarbitone and breathed spontaneously through an endotracheal tube. A catheter was inserted into one of the femoral arteries and the tip of the catheter was placed in one of the renal arteries. During one hour the dogs received a varying number of unilateral selec-

tive renal artery injections of metrizoate (370 mg iodine/ml; Table 3) under fluoroscopy. The total material of 22 dogs was divided into eight groups (Fig. 6) and in six of these groups the dogs were sacrificed one hour after the last contrast medium injection and in two groups after 48 hours for investigations of the kidneys. The size of each single injection is called "single dose" and the summation of all "single doses" given to one dog is called "total dose". The size of the "single doses" and the "total dose" used in each group is given in Fig. 6.

The non-injected kidney served as a control. Fourteen dogs received right renal artery injections and eight dogs left

SINGLE DOSE ml/kg	TIME OF SACRIFICE AFTER CONTRAST MEDIUM INJECTION					
	1 HOUR			48 HOURS		
1.0-2.0	3	4	3	5	1	
	(3)	(4)	(3)	(3)	(1)	
0.2-0.5	1	3	2			
	(0)	(0)	(0)			
	2	5	10	2	5	TOTAL DOSE ml/kg

Fig. 6. The total material of 22 dogs was divided into eight different groups according to this figure. The dogs were injected with various single and total doses (ml/kg b.w.) of metrizoate into one renal artery during one hour. Sixteen dogs were sacrificed one hour after the last contrast medium injection and six dogs were sacrificed 48 hours postinjection for further investigations of the kidneys.

Numbers within parentheses are numbers of dogs developing irregular nephrograms (patchy contrast medium retention) in the injected kidney. (In the text "large single doses" refer to 1.0-2.0 ml/kg b.w. whereas "small single doses" refer to 0.2-0.5 ml/kg b.w.).

renal artery injections.

After the last contrast medium injection, fluoroscopy was used to determine whether the nephrogram was homogeneous or irregular (non-homogeneous), the latter is here called "patchy contrast medium retention" (these nephrograms were similar to those produced by diatrizoate in paper II; Fig. 4a and b).

After sacrificing the dogs all kidneys were removed and weighed. The cranial and caudal thirds of each kidney were homogenized and their Cr-51 and I-125 activities were determined in a scintillation counter and expressed in counts per min per gram wet tissue. In each dog the ratio "Cr-51 activity in injected kidney/Cr-51 activity in non-injected kidney" was calculated and this ratio is here called "relative platelet accumulation". Analogously, "relative kidney weight" and "relative fibrinogen accumulation" were calculated from kidney weights and I-125 activities, respectively. From the middle third of each kidney specimens were prepared for a blind histologic evaluation with special references to thrombi in the vessels.

Results. Patchy contrast medium retention in the injected kidney was significantly more frequent in the 16 dogs that had received large single doses (1-2 ml/kg b.w.) of metrizoate (frequency 14/16) than in the six dogs that had received small single doses (0.2-0.5 ml/kg b.w.) (frequency 0/6) (Fig. 6).

There was no significant difference in frequency of patchy contrast medium retention between the five dogs that had received the largest total dose (10 ml/kg b.w.) (frequency 3/5) and the nine dogs that had received the smallest total dose (2 ml/kg b.w.) (frequency 6/9) (Fig. 6).

The relative platelet accumulation (RPA) and the relative kidney weight (RKW) when determined one hour postinjection were both significantly higher in the ten dogs that had received

large single doses of the contrast medium and also had patchy contrast medium retention than in the six dogs that had received small single doses of the contrast medium and also had homogeneous nephrograms (Fig. 7).

The relative platelet accumulation and the relative kidney weight, when determined 48 hours postinjection in six dogs that had received large single doses of contrast medium, were both significantly lower than in the ten dogs that also had received large single doses, but, in which RPA and RKW were determined one hour postinjection (Fig. 7).

The results regarding the relative fibrinogen accumulation are given in Fig. 7.

Microscopic examination of kidney specimens from dogs sacrificed one hour postinjection revealed no abnormalities in the 16 control kidneys and in the six kidneys injected with small single doses.

Thrombi in the renal vessels were found in specimens from all ten kidneys injected with large single doses and investigated one hour postinjection (Fig. 7). The distribution of the thrombi was irregular. Areas with thrombi were intermingled among areas with normal microscopic appearance. Thrombi were localized in the afferent arterioles and in the glomerular capillary tufts. In the kidneys with the highest values of RPA, thrombi were found in the afferent arterioles and red blood cells were present in the vessel walls. The corresponding glomerular loops were completely obstructed by thrombi (Paper III, Fig. 4a, b). Microscopically, the thrombi appeared to consist mainly of platelets. Occasionally, formation of fibrin in association with the platelets could be demonstrated (paper III, Fig. 4c). In the kidneys with the lowest values of RPA in these groups, platelet aggregates or only small scattered thrombi were found in the glomerular capillary tufts (paper III, Fig. 4d). In these specimens no thrombi were found in the

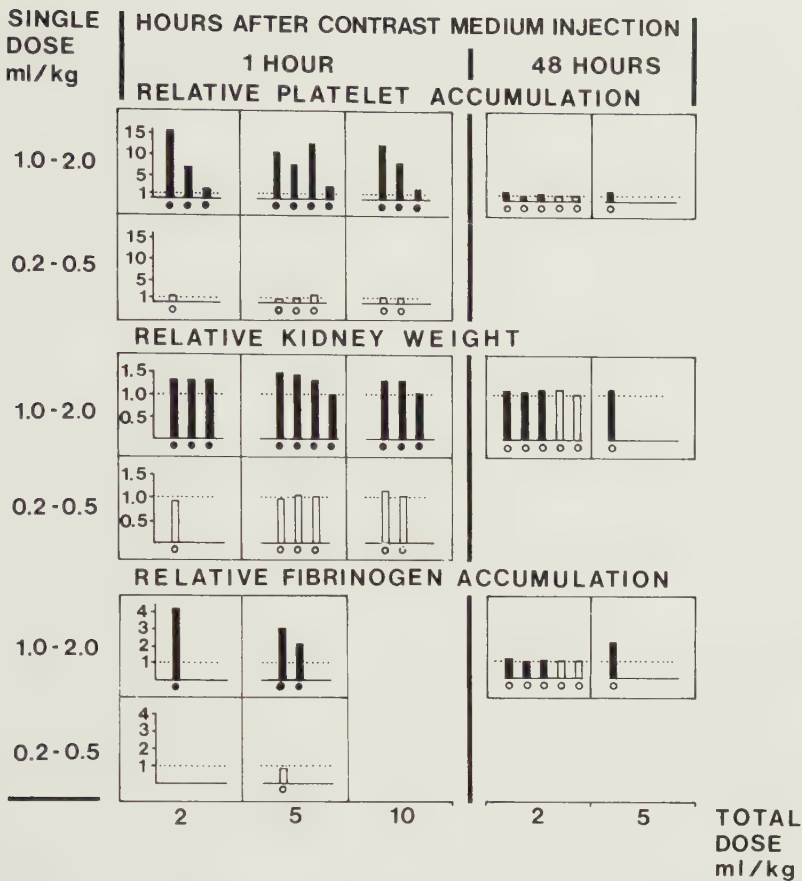


Fig. 7. This figure shows the parameters, which were determined following selective unilateral renal artery injections of various doses of metrizoate.

White columns represent injected kidneys with homogeneous nephrograms.

Black columns represent injected kidneys with patchy contrast medium retention.

The height of each column represents a ratio value in one dog, i.e.; ratio injected/non-injected kidney for Cr-51 activities, kidney weights, and I-125 activities here called relative platelet accumulation, relative kidney weight, and relative fibrinogen accumulation, respectively. Relative platelet accumulation and relative kidney weight were both determined one and 48 hours postinjection in 16 and 6 dogs, respectively. Relative fibrinogen accumulation was determined one and 48 hours postinjection in 4 and 6 dogs, respectively.

White circles represent injected kidneys without microscopically demonstrable thrombi.

Black circles represent injected kidneys with microscopically demonstrable thrombi.

Each dog is represented in the same position in the three different histograms.

afferent arterioles.

Microscopic examination of kidney specimens from dogs sacrificed 48 hours postinjection revealed no abnormalities in the six control kidneys and in two of the injected kidneys. In four injected kidneys there were irregular distributed tubular lesions among areas with normal tubular epithelium. These lesions ranged from hydropic degeneration to cellular dissolution, with frank necrosis of the tubular epithelium. The tubules were frequently dilated and lined with flattened epithelium. Tubular casts composed of altered epithelial cells, red blood cells, and amorphous material, which might represent proteins, were frequently seen. There were no thrombi or other vascular lesions.

Paper V: RENAL ANGIOGRAPHY WITH IOHEXOL AND METRIZOATE

Material and methods. Adult patients referred for nephroangiography were eligible for the investigation. Patients with serum creatinine levels above 125 $\mu\text{mol/l}$ and patients who had received injection of contrast medium within 48 hours prior to angiography were excluded from the studies on renal function. Using a semiselective and selective technique, nephroangiography with metrizoate (280 mg iodine/ml, Table 3) was performed in 15 patients and then 15 patients were examined with iohexol (300 mg iodine/ml, Table 3). As regards total contrast medium doses and doses selectively injected into the renal arteries, there were no significant differences between the groups. Cr-51-EDTA clearance and serum creatinine were determined the day before and the day after nephroangiography. Urine samples were taken the day before, as soon as possible after angiography (0.5-4 hours), and the day after angiography for analyses of albumin and creatinine.

Results. The laboratory findings are given in Table 7. The numbers of patients included in the various calculations are

given in Table 7 (three patients were excluded according to the exclusion criteria and data from five other patients were incomplete). When measured the day after nephroangiography with metrizoate and iohexol, the values of ^{51}Cr -EDTA clearance did not differ significantly from the preangiographic values. Serum creatinine was unaffected in the iohexol group, whereas there was a statistically significant increase in serum creatinine the day after nephroangiography in the metrizoate group. In the metrizoate group there was also a transient increase in urinary albumin concentrations, whereas this parameter was unaffected in the iohexol group.

Table 7. Laboratory findings

Study	Contrast Medium	No. Patients	Preangiographic		Postangiographic	
			Day before (Median & Range)		1/2-4 hrs After (Median & Range)	
Cr-51-EDTA clearance (ml/min)	Metrizoate	11	75 (35-129)	-	-	82 (46-137)
	Iohexol	15	94 (60-137)	-	-	93 (57-151)
Serum creatinine ($\mu\text{mol/l}$)	Metrizoate	11	114 (65-124)	-	-	119* (73-164)
	Iohexol	12	91 (69-125)	-	-	88 (71-124)
Urine albumin (g albumin/ g creatinine)	Metrizoate	10	0.043 (0.0072-0.18)	1.5 [†] (0.014-22)	0.071 (0.0075-1.6)	0.015 (0.0081-0.64)
	Iohexol	14	0.028 (0.0068-0.98)	0.050 (0.0060-0.62)	0.015 (0.0081-0.64)	0.015 (0.0081-0.64)

* $p < 0.05$ compared with preangiographic values.[†] $p < 0.01$ compared with preangiographic values.

GENERAL DISCUSSION

In the present investigation, aimed to find effects of ratio 1.5 contrast media that may be involved in contrast medium-induced acute renal failure and to find contrast media with lower nephrotoxicity than that of the ratio 1.5 media, the following main strategies were chosen:

1. Choice of contrast media. Diatrizoate and metrizoate were chosen to represent the commonly used ionic ratio 1.5 contrast media. Metrizamide, the first non-ionic contrast medium, which may have a nephrotoxicity approximately the same as that of ratio 1.5 media, was included in one experimental model. Iohexol was chosen for special evaluation to represent the second generation of non-ionic ratio 3.0 contrast media, because it had been demonstrated that this medium had the lowest intravenous and subarachnoid toxicity of the ratio 3.0 contrast media that were available at the time of the planning of the separate investigations (4, 28). Effects on the glomerular membrane, however, were evaluated using different non-ionic and ionic ratio 3.0 contrast media.

2. Administration of contrast media. Selective renal artery injections were used in all investigations. This way of administering the contrast media was chosen because it is probably the most noxious way of giving a potentially nephrotoxic substance.

3. Dosage of contrast media. In the animal experiments mainly large contrast medium doses were used (0.5-2 ml/kg b.w.; 370 mg iodine/ml) - doses greatly exceeding those generally used for selective renal artery injections in humans. Large doses were chosen to study irregular nephrograms (II-IV), which had been observed at these dose levels. Moreover, large doses and selective renal artery injections are more likely to produce nephrotoxic reactions and may increase the possibilities to discriminate between different contrast media with regard to

their nephrotoxicity.

Some possible disadvantages of the two latter strategies should be considered. It is not known whether acute renal failure following selective renal artery injections of a contrast medium represents a type of renal failure that is different from that which may occur after intravenous administration or non-renal angiography. If so, the results from the present investigation would only be relevant with regard to nephrotoxicity following nephroangiography. Results obtained with large contrast medium doses, exceeding those used in clinical nephroangiography, may not be relevant to the clinical situation. However, it is possible that effects on the kidneys, demonstrated with large contrast medium doses in animals with healthy kidneys, may have a pathogenetic importance for contrast medium-induced acute renal failure, when smaller clinical doses are used in patients with vulnerable kidneys; for instance, those with diabetes mellitus and previous renal insufficiency and those with transplanted kidneys.

Effects on the glomerular membrane

Two patients who reacted with transient massive albuminuria and one of them with temporary renal failure were the incentive for HOLTAS et coll. to further evaluate postangiographic albuminuria (93). They found that transient albuminuria frequently occurred after nephroangiography with ionic metrizoate and diatrizoate and non-ionic metrizamide in both man and dog (36, 38, 39, 47, 92). The effect was attributed to an increased permeability of the glomerular membrane (92) and the albuminuria was related to the chemical structure of the contrast medium rather than to its osmolality (37). In these investigations urine samples from the bladder were mainly used and therefore the albuminuria from each kidney could not be evaluated.

The present results showed that the second generation of non-ionic ratio 3.0 contrast media and the ionic ratio 3.0 medium ioxaglate also produce postangiographic albuminuria in dogs but to a smaller extent than the ratio 1.5 contrast medium diatrizoate (I) and iothexol produced less albuminuria than the ratio 3.0 medium metrizamide (IV). The albuminuria was related to selective renal artery injections. This was demonstrated using separate ureter catheters and selective unilateral contrast medium injections, which did not produce any albuminuria from the non-injected kidneys (II, IV). These results also exclude the ureter catheters as the cause of the albuminuria and the macroscopic hematuria because there was no albuminuria or macroscopic hematuria from the non-injected kidneys. However, macroscopic hematuria was frequently observed in urine samples from diatrizoate- and metrizamide-injected kidneys (II, IV), whereas such hematuria was only observed in urine samples from one of nine kidneys injected with iothexol (IV). The origin of the macroscopic hematuria is unknown, but it may be caused by severe damage to the glomerula.

Iothexol, when used in clinical nephroangiography, did not produce albuminuria, whereas metrizoate produced a transient glomerular leakage (V). Like iothexol, ioxaglate did not produce albuminuria in clinical nephroangiography (68).

The significance of postangiographic albuminuria in contrast medium-induced acute renal failure is not known. However, disturbances in glomerular permeability, although transient, must be considered when discussing pathogenetic mechanisms, such as intratubular obstruction of precipitated material, and some reports suggest that this might be a major pathogenetic factor (8, 93). The albuminuria was caused by selective renal artery injections of the contrast medium and therefore albuminuria may be excluded, when considering the pathogenesis of renal failure following intravenous administration of the contrast medium or non-renal angiography. However, proteinuria following intravenous administration of contrast medium has

been reported (66) and contrast medium effects on the glomerular membrane of patients with preexisting renal damage is not known.

Effects on nephrograms and renal hemodynamics

The present investigation showed that selective renal artery injections of large single doses (1-2 ml/kg b.w.; 370 mg iodine/ml) of diatrizoate and metrizoate produced, at a high frequency, patchy contrast medium retention. This irregular nephrogram was associated with:

1. a marked reduction in renal blood flow (RBF); (II)
2. a transient accumulation of platelets in the kidney; (III)
3. a transient accumulation of fibrinogen in the kidney; (III)
4. a transient increase in kidney weight; (III)
5. microscopically demonstrable transient platelet aggregates and thrombi in glomerular capillary tufts and in afferent arterioles; (III)
6. tubular damage, which was demonstrable after the transient formation of thrombi. (III)

Selective renal artery injections of small single doses (0.2-0.5 ml/kg b.w.; 370 mg iodine/ml) of metrizoate produced homogeneous nephrograms and no signs of thrombus formation.

Ionic ratio 1.5 contrast media may cause endothelial damage (69), and this injury may predispose to thrombus formation (14, 78). Such an injury may be related to the present results, which may be interpreted as follows: Large single doses of the ionic ratio 1.5 contrast medium cause damage to the vascular endothelium on which platelets and subsequently fibrinogen accumulate producing microscopically demonstrable thrombi. These may cause a reduction in renal blood flow by obstruction of the vessel lumen but also by release of vasoactive substances, such as serotonin, from the platelets (24, 77). The

increased kidney weight is interpreted as fluid retention, a part of which is the abnormally retained contrast medium and another part might be edema caused by disturbances in the microcirculation.

The transient nature of these hemodynamic events (factors 1-5 above) were indicated by high values of relative platelet accumulation, relative fibrinogen accumulation, relative kidney weight, and the presence of histologically demonstrable thrombi in kidneys examined one hour postinjection and by subsequent low values of these parameters and no histologically demonstrable thrombi in kidneys examined 48 hours postinjection. When RBF was directly measured in diatrizoate-injected kidneys with patchy contrast medium retention (II), the decrease in RBF was most pronounced 5 and 15 min postinjection and then RBF subsequently increased 120 and 210 min postinjection. Regression of the vascular lesions might be due to thrombolytic mechanisms and restoration of renal blood flow.

Platelet accumulation and thrombus formation on intravascular catheters have been demonstrated in dogs (41) and represent a potential source of thromboembolism. However, platelet emboli from the catheters do not seem to be a major factor affecting the present results, because in all the dogs the catheter had been placed in a renal artery during a period of equal length and there were no signs of thrombi in the dogs receiving small single doses of the contrast medium.

Primary contrast medium-induced aggregation of the platelets in the general vascular bed associated with secondary trapping of the platelet aggregates in the kidney is not a plausible explanation of the present results, as there were no thrombi in the control kidneys.

Reports of contrast medium interaction with platelet function are contradictory and, contrary to the present investigation (III), most reports deal with in vitro experiments. Inhibition

of platelet aggregation has been reported in studies using aggregometers (17, 85, 102), whereas platelet aggregation was found in studies using microscopy (24, 100). Contrast medium-induced release of serotonin from platelets has been reported (24, 77), whereas others found inhibition of serotonin release (102).

The relation between the doses of metrizoate and the effects suggesting intrarenal thrombus formation (III) shows that the kidney may tolerate a large total dose of the contrast medium administered as several small single doses without platelet aggregation and thrombus formation. On the other hand, a much smaller total dose might induce thrombus formation when injected in one or a few large single doses. These results might be explained by a hypothesis that assumes that when the contrast medium concentration exceeds a certain value in the cell membrane and/or in the interior of endothelial cells these cells become damaged to such a degree that platelet adhesion and aggregation are induced on their surfaces as the first step in thrombus formation. For a damaging contrast medium concentration to arise, a certain period of contact is necessary between the contrast medium in the vessel lumen and the surfaces of the endothelial cells. Therefore, a large single dose (with a long period of contact) could lead to a damaging concentration, whereas small single doses (with short periods of contact) might not, because the contrast medium concentration in the cells might decrease between the injections when blood instead of contrast medium flows over them.

Selective renal artery injections of iodine-equivalent large doses of metrizamide and iohexol produced homogeneous nephrograms and no marked effects on renal blood flow (IV). It has been shown that metrizamide and iohexol produce less endothelial damage than the ratio 1.5 media (69). This difference may imply a reduced risk of formation of microthrombi following injections of metrizamide and iohexol and may explain the homogeneous nephrograms and the lack of marked effects on renal

blood flow produced by metrizamide and iohexol on the one hand (IV) and the patchy contrast medium retention produced by diatrizoate (II) and metrizoate (III), the marked reduction in RBF produced by diatrizoate (II), and the thrombus formation produced by metrizoate (III), on the other.

Irregular distribution and abnormal retention of the contrast medium in the renal parenchyma following selective renal artery injections of diatrizoate have previously been described (63, 86), and in these reports hemodynamic disturbances were also suggested as a possible etiologic factor. Irregular post-angiographic nephrograms have also been reported following temporary occlusion of the renal artery (70) and following hemorrhagic hypotension (49). Recently, it has been demonstrated that selective renal artery injections of diatrizoate and iopamidol in dogs, combined with occlusion of the renal artery, produce irregular nephrograms, but this effect was less pronounced in iopamidol-injected kidneys; moreover, iopamidol produced less microscopically demonstrable glomerular and tubular damage than diatrizoate (56). In that investigation renal blood flow was measured by a radioactive microsphere technique, and it was concluded that flow changes could not explain the varying severity of glomerular and tubular damage.

In the present investigation (III) tubular damage was found in four of six dogs examined 48 hours postinjection and at that time there were no signs of thrombi. Whether this tubular damage is secondary to the hemodynamic effects and/or also represents a "direct toxic" effect of the contrast medium on the tubules is an unsolved question. These results also demonstrate that there is a risk of misinterpreting the contrast medium effects. If microscopic examination had only been performed one hour after the contrast medium injection merely vascular lesions (thrombi) would have been found, whereas if microscopic investigation had only been performed 48 hours postinjection no thrombi and merely tubular damage would have been found.

Reversible renal failure associated with abnormal retention of contrast medium, demonstrated by computed tomography, following percutaneous transluminal angioplasty in humans has been reported (98). During this procedure, the renal vascular bed may be exposed to a hyperosmolar contrast medium in high concentration for periods of varying length when perfusion is completely obstructed by the inflated balloon catheter, and the total effect might be deleterious to the vascular endothelium.

Previous investigations with electromagnetic flow meters on effects of selective renal artery injections of ratio 1.5 contrast media on renal blood flow (RBF) in dogs have dealt with short-term effects and have demonstrated a biphasic response with a short increase (less than 1 min) and then a longer decrease (less than 15 min) in RBF (16, 42, 43, 80, 87). The results from the present investigation (II) demonstrated a prolonged reduction in RBF following injections of diatrizoate, a discrepancy that might be related to higher contrast medium doses used in the present investigation. In agreement with the present results, metrizamide produced less pronounced hemodynamic effects than diatrizoate when used in nephroangiography in dogs (64).

Effects on glomerular filtration rate (GFR) and the osmotic diuresis

The present results showed that selective renal artery injections of large doses of diatrizoate (3×1 ml/kg b.w.; 370 mg iodine/ml) in dogs produced a marked decrease in GFR in the immediate postangiographic period, whereas iodine-equivalent doses of metrizamide and iohexol did not (II, IV). In the diatrizoate-injected dogs these injections produced a lower osmotic diuresis from the injected kidneys compared with the non-injected ones, whereas metrizamide, iohexol, and mannitol produced a higher osmotic diuresis from the injected kidneys compared with the non-injected ones. A diatrizoate-induced

dysfunction of the injected kidneys was thus indicated by both a decrease in GFR and the relatively lower osmotic diuresis from the injected kidneys.

In agreement with the present results, contrast medium-induced reduction in GFR has been reported following selective renal artery injections of diatrizoate in dogs (43, 67). Severe azotemia, in some instances fatal, and extensive histologic changes in the kidneys have been observed following selective renal artery injections of iothalamate in dogs (76). Moreover, reductions in GFR following intravenous injections of diatrizoate in dogs and rats have been reported (23, 75). In accordance with the present results, the ratio 1.5 contrast medium iothalamate produced a marked decrease in creatinine clearance during the first 15 min after intravenous injection in dogs, whereas metrizamide did not (97).

In nephroangiography performed in patients with normal serum creatinine ($<125 \mu\text{mol/l}$), neither metrizoate nor iohexol affected GFR as measured by Cr-51-EDTA clearance on the day after angiography (V). Serum creatinine, which is also an expression of GFR, was not affected by nephroangiography with iohexol; but in the metrizoate group there was a slight but significant increase in serum creatinine level the day after angiography. Thus, the results of the two methods estimating GFR were contradictory in the metrizoate group. Cr-51-EDTA clearance is a more reliable expression of GFR than the serum creatinine level, and it is concluded that there is no effect on GFR when measured the day after nephroangiography with iohexol or metrizoate.

The increased level of serum creatinine the day after nephroangiography in the metrizoate group could be explained by a transient decrease in GFR in the immediate postangiographic period. The serum creatinine level depends on previous renal function; after a transient decrease in GFR there is a time delay before the serum creatinine returns to the preangio-

graphic level. Cr-51-EDTA clearance reflects glomerular filtration rate during the measuring period independent of previous function.

A slight, but significant increase in serum creatinine was also found in a review of two previous clinical trials in nephroangiography performed using the same technique and with metrizoate in the same concentration (V).

In agreement with the present results, an increase in serum creatinine following clinical nephroangiography with the ionic ratio 1.5 medium diatrizoate has been reported, whereas the non-ionic ratio 3.0 iopamidol did not produce a significant increase in serum creatinine (44). In that investigation, enzymuria, as an indicator of tubular injury, was also used, and such was produced by diatrizoate, whereas iopamidol did not.

In summary, the present results (II, IV, V) indicate that selective renal artery injections of ionic ratio 1.5 media may produce a decrease in GFR in both healthy dogs and patients with normal serum creatinine, whereas iothexol does not affect GFR.

It may be argued that the slight, but statistically significant increase in serum creatinine in the metrizoate group in paper V and in the reviewed clinical trials (V) is of no clinical importance. However, this "slight" effect in individuals with normal renal function may have another clinical presentation when ionic contrast media are used in patients with impaired renal function. Therefore, the advantage of metrizamide and iothexol demonstrated by lack of effects on GFR should not be underestimated as this may imply a reduced risk of contrast medium-induced acute renal failure when compared to ratio 1.5 media (II, IV, V).

GENERAL SUMMARY AND CONCLUSIONS

1. - Postangiographic albuminuria - a sign of increased permeability of the glomerular membrane - is caused by selective renal artery injections of a contrast medium and can be produced by both ratio 1.5 and ratio 3.0 contrast media in dogs.
 - The ratio 3.0 contrast media iopamidol, iohexol, and ioxaglate affect glomerular permeability less than the ratio 1.5 medium diatrizoate and the ratio 3.0 medium metrizamide in dogs.
 - Iohexol does not affect glomerular permeability in clinical nephroangiography, whereas metrizoate produces a transient increase in glomerular permeability.
2. - Selective renal artery injections of large single doses of ionic diatrizoate and metrizoate in dogs produce, at a high frequency, an irregular nephrogram; "patchy contrast medium retention", which is:
 - caused by large single doses of the ionic ratio 1.5 contrast medium but not by a large total dose when injected as several small single doses;
 - associated with a decrease in renal blood flow and a transient thrombus formation in glomerular capillary tufts and afferent arterioles.
- The transient thrombus formation may be followed by tubular damage.
- In clinical nephroangiography the size of the single dose injected into a renal artery should be kept as small as possible to decrease the risk of thrombus formation.
- Selective renal artery injections of iodine-equivalent large single doses of non-ionic metrizamide and iohexol in dogs produce homogeneous nephrograms and no marked effects on renal blood flow. This may imply a reduced risk of intrarenal thrombus formation when compared with ionic ratio 1.5 media.

3. - Selective renal artery injections of large doses of diatrizoate in dogs produce a marked decrease in glomerular filtration rate (GFR) and a reduced osmotic diuresis, whereas iodine-equivalent doses of metrizamide and iohexol do not affect GFR and produce a "normal" osmotic diuresis.
 - Metrizoate produces a transient decrease in GFR in clinical nephroangiography, whereas iohexol does not affect GFR.
4. - The non-ionic ratio 3.0 contrast medium iohexol interferes less with several parameters of renal function than ionic ratio 1.5 media both in experimental and clinical nephroangiography. This suggests that the nephrotoxicity of iohexol is less than that of the ratio 1.5 media. This may imply that the future use of the second generation of ratio 3.0 contrast media in humans means a reduced risk of contrast medium-induced acute renal failure when compared with the use of ionic ratio 1.5 media.

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PROTEINURIA FOLLOWING NEPHROANGIOGRAPHY

VII. Comparison between ionic monomeric, monoacidic dimeric and non-ionic contrast media in the dog

CARL TÖRNQUIST, TORSTEN ALMÉN, KLAES GOLMAN and STIG HOLTÅS

The nephrotoxicity of the tri-iodinated contrast media in common use today has been considered very low and almost negligible and angiography is nowadays performed also in patients with severely impaired renal function (ABRAMS 1971). However, in recent years an increasing number of reports on contrast medium-induced renal failure has appeared in the literature and pre-existing renal insufficiency and diabetes mellitus have been regarded as important risk factors as reviewed by BYRD & SHERMAN (1979). Although the renal failure in these series was mostly transient and present already before angiography in patients with diseases affecting the kidneys, they elucidate the importance of not underestimating the risk of contrast medium-induced renal failure.

Proteinuria is one indication of renal injury and it has recently been demonstrated that it frequently occurs after nephroangiography with metrizoate in man (TEJLER et coll. 1977 a) and in the dog, following injection of metrizoate and diatrizoate (HOLTÅS et coll. 1978 a). Analyses of the molecular sizes of the excreted proteins demonstrated that the contrast media increase the glomerular permeability. In attempts to evaluate the proteinuria in the dog it was shown that the chemical structure of the contrast medium was of greater importance in causing proteinuria than the high osmolality of the contrast medium solution (HOLTÅS et coll. 1978 b, HOLTÅS & TEJLER 1979).

The degrees of albuminuria induced by five differ-

ent contrast media were compared: the commonly used ionic monomeric diatrizoate, the recently synthesized non-ionic iopamidol, iohexol and C29 and the monoacidic dimeric contrast medium ioxaglate.

Material and Methods

Mongrel dogs, weighing on the average 20 kg (12–35 kg), anaesthetized with intravenous pentobarbitone (Mebumal, ACO) and spontaneously breathing through an endotracheal tube, had a transurethral catheter introduced into the bladder. In each dog selective unilateral nephroangiography was performed with manual injection of contrast medium (0.5 ml/kg, 370 mg I/ml). After an average period of 10 days (3–32 days) the nephroangiography was repeated, but then with injection of another medium into the other kidney. Arterial and urinary bladder catheterizations were performed as previously described (HOLTÅS et coll. 1978 a).

The dogs were divided into 3 groups. In each group, the changes in the concentration of urinary albumin were recorded following injection of two different contrast media. The order of injection was randomized. In group I the number of dogs was 10 and the contrast media diatrizoate-iopamidol, in group II 24 dogs and diatrizoate-iohexol, in group III 9 dogs and C29-ioxaglate. For all contrast media the iodine concentration was 370 mg/ml and the dose 0.5 ml/kg. The chemical structures and the osmolalities for solutions of sodium/meglumine dia-

Table

Preangiographic and maximum postangiographic concentration of urinary albumin in gram albumin per gram urinary creatinine. Median concentration and range

Group	Contrast medium	Concentration of albumin in urine	
		Before angiography	After angiography
I	Diatrizoate	0.033 (0.0080–0.090)	27 (1.22–124)
	Iopamidol	0.024 (0.011–0.084)	1.2 (0.14–71)
II	Diatrizoate	0.034 (0.0060–0.57)	11 (0.20–180)
	Iohexol	0.064 (0.0036–0.96)	2.1 (0.12–18)
III	C29	0.030 (0.012–0.10)	0.67 (0.058–14)
	Ioxaglate	0.015 (0.0064–0.074)	2.5 (0.14–17)

trizoate, iopamidol, iohexol, C29 and sodium ioxaglate are given by HAAVALDSEN (1980).

Blood was taken before and urine samples before and 15, 30 and 60 min after each angiography. The concentration of albumin and creatinine in urine and plasma was determined as previously described (HOLTÅS et coll. 1978 a). For the immunologic determination of albumin concentration pooled canine plasma with a concentration of 35.4 g/l was used as standard. The urinary albumin concentration was expressed per gram of urinary creatinine thereby relating albumin excretion to glomerular filtration rate.

When comparing the albuminuric effects of the different contrast media the maximum concentration of urinary albumin following nephroangiography has been used in the statistical evaluation. Differences were considered significant when p -values <0.05 were obtained by the Mann-Whitney rank sum test or Wilcoxon's test for paired observations.

Results

No significant differences in the concentration of urinary albumin existed before injection in the groups. The concentration of creatinine and albumin in plasma remained within normal limits throughout the experiments. All contrast media induced significant increases ($p<0.01$) of urinary albumin concentration following nephroangiography.

Following injection of diatrizoate in groups I and II the median urinary albumin concentration increased 820 and 320 times, respectively. After injection of iopamidol, iohexol and C29 the median concentration of urinary albumin increased 50, 33 and 22 times, respectively, and after injection of ioxa-

glate 170 times. The concentration of albumin became higher in urine than in plasma in 8 of the 34 dogs injected with diatrizoate. Such high concentrations of urinary albumin never occurred after injection of the other contrast media.

The maximum urinary albumin concentration following injection of diatrizoate was significantly higher than following injection of iopamidol or iohexol ($p<0.01$ paired comparisons). No significant difference in the degree of postangiographic albuminuria was found between C29 and ioxaglate (paired comparisons).

When comparing the degrees of postangiographic albuminuria induced by iopamidol, iohexol, C29 and ioxaglate (unpaired comparisons) no significant differences were found. C29 and ioxaglate induced significantly less albuminuria than diatrizoate in groups I and II (unpaired comparisons, C29-diatrizoate: $p<0.01$, ioxaglate-diatrizoate: $p<0.02$). The results are summarized in the Table.

Discussion

Previously it has been demonstrated that diatrizoate and C29 in the dog induced albuminuria following nephroangiography (HOLTÅS & TEJLER). This is confirmed by the present results, which also show that the contrast media iopamidol, iohexol and ioxaglate induce postangiographic albuminuria. The albuminuria caused by diatrizoate was sometimes extremely high and 8 of 34 dogs developed such high albumin concentrations in urine that they exceeded their albumin concentration in plasma, whereas iopamidol, iohexol, C29 and ioxaglate never caused such massive albuminuria.

At an iodine concentration of 370 mg/ml the osmolality of diatrizoate is two to three times higher

than that of the other contrast media. The difference in osmolality might therefore appear to be the major factor causing the significantly higher postangiographic albuminuria induced by diatrizoate than by iopamidol, iohexol, C29 and ioxaglate. However, previously it has been shown that the non-ionic contrast medium metrizamide, which has about one third of the osmolality of diatrizoate at equal iodine concentration, produced the same degree of postangiographic albuminuria as diatrizoate (HOLTÅS & TEJLER, HOLTÅS *et coll.* 1980). Furthermore, a sodium chloride solution equally hypertonic as diatrizoate caused significantly less albuminuria than diatrizoate following injection into a renal artery (HOLTÅS *et coll.* 1978 b). These results may indicate that high osmolality of contrast medium solutions is only a minor factor causing postangiographic albuminuria and that the chemical structure of the contrast medium is probably a more important factor.

Wide variations have been found between different individuals in the degree of postangiographic albuminuria both in man and in the dog, and this has been a disadvantage in the evaluation of possible differences between contrast media. As the kidney is a paired organ this disadvantage can be reduced by comparing the degree of postangiographic proteinuria induced by different contrast media in the same individual as was performed between diatrizoate-iopamidol, diatrizoate-iohexol and C29-ioxaglate in the present series.

Postangiographic proteinuria certainly represents a renal dysfunction but its role in the development of postangiographic renal failure is uncertain. The mechanism causing such renal failure might in some cases be tubular blockage by precipitated urinary proteins as was the probable mechanism in one case reported previously (TEJLER *et coll.* 1977 b). If this is the most important mechanism causing contrast medium-induced renal failure, the most accurate way of estimating postangiographic proteinuria would be to give the absolute concentration of protein in urine because this would be an evaluation of the risk of protein precipitation in the tubuli.

However, the absolute concentration of protein in urine is not a reliable estimation of the amount of protein leaking through the glomeruli because the same amount of protein leakage will give different protein concentrations in the urine with varying diuresis. When compensation for variations in diuresis is made by giving protein concentration per gram of urinary creatinine this will represent an evalua-

tion of the amount of protein leaking through the glomeruli which means an evaluation of glomerular injury. As the mechanisms behind contrast medium-induced renal failure still are obscure, the degree of albuminuria following nephroangiography was expressed per gram of urinary creatinine in the present investigation, thus representing the glomerular leakage of protein which is more related to the glomerular injury than to the risk of protein precipitation in the tubuli.

The maximum concentration of urinary albumin per gram creatinine following nephroangiography was used in the comparisons, whereas the quotient between maximum postangiographic and preangiographic concentration (relative increase of urinary albumin) has been used previously in the dog (HOLTÅS *et coll.* 1978 a, b, HOLTÅS & TEJLER). Urinary albumin concentration is usually very low before angiography (about 0.1 per cent of the plasma concentration) and could therefore be influenced by minor bleeding caused by the catheter in the urinary bladder. On the other hand, the influence on the high postangiographic concentrations of albumin will be negligible. Therefore, it was decided in the present investigation to use the maximum concentration of urinary albumin per gram creatinine following nephroangiography for comparisons instead of relative increase of urinary albumin.

Transient contrast medium-induced renal failure has in some recently presented materials been reported to occur in a frequency of about 10 per cent following angiography and pre-existing renal insufficiency and diabetes mellitus have been regarded as important risk factors (OLDER *et coll.* 1976, SWARTZ *et coll.* 1978, BYRD & SHERMAN). Probably only a small risk of contrast medium-induced renal failure exists in patients with normal renal function before angiography but nephroangiography may be performed in patients with diseased or vulnerable kidneys, as for instance after renal transplantation. It is important to reduce the risk of contrast medium-induced renal failure and contrast media intended for nephroangiography should affect renal function as little as possible. Postangiographic proteinuria is an indication of renal dysfunction and should therefore be avoided. The present investigation demonstrates that it is possible to reduce the postangiographic proteinuria caused by, for instance, diatrizoate as demonstrated by the significantly lower postangiographic albuminuria induced by iopamidol, iohexol, C29 or ioxaglate.

SUMMARY

The degrees of albuminuria induced by nephroangiography in dogs with the ionic monomeric contrast medium diatrizoate, the non-ionic iopamidol, iohexol and C29 and the monoacidic dimeric contrast medium ioxaglate were compared. Diatrizoate induced significantly higher albuminuria than the other contrast media. No significant differences in the degree of albuminuria following angiography were found between iopamidol, iohexol, C29 and ioxaglate.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Medical Faculty, University of Lund, the Swedish Medical Research Council (Project No. 3483) and the Segerfalk foundation. The expert technical assistance of Anita Burnett, Georg Hansson, Britt-Marie Lilja and Gail Åkerman is gratefully acknowledged.

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RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH DIATRIZOATE

Effects of saline, mannitol, and diatrizoate on renal blood flow,
glomerular permeability and filtration rate
and diuresis in dogs

C. TÖRNQUIST, T. ALMÉN, K. GOLMAN and S. HOLTÅS

Abstract

The ionic contrast medium diatrizoate used in high-dose unilateral nephroangiography in dogs produced an abnormal nephrogram, 'patchy contrast medium retention', and a marked decrease in renal blood flow in five of eight injected kidneys. Increased glomerular permeability (albuminuria), reduced glomerular filtration rate (creatinine clearance), and reduced osmotic diuresis were demonstrated in all selectively injected kidneys.

Clinical reports on acute renal failure following intravascular administration of water-soluble contrast media (2, 6, 18) are creating a growing interest in the nephrotoxicity of the commonly used ionic tri-iodinated ratio 1.5 contrast media (i.e., diatrizoate, iodamide, iothalamate, ioxithalamate and metrizoate). Contrast medium-induced acute renal failure may occur following intravenous injection, as well as after selective renal artery injection. These two ways of administering the contrast medium might imply different effects on the kidneys due to differences in concentration of the contrast medium in the renal vascular bed. Although a number of mechanisms have been suggested, the pathogenesis of contrast medium-induced acute renal failure remains incompletely known (2, 5, 6, 13, 18).

Transient postangiographic albuminuria, caused by an increased permeability of the glomerular

membrane, frequently occurs after nephroangiography with metrizoate, diatrizoate and metrizamide in both man and dog (8, 9, 11, 14, 27), but its role in the etiology of contrast medium-induced acute renal failure is not known.

In a previous preliminary investigation dealing with postangiographic albuminuria in dogs, we occasionally observed an irregular (non-homogeneous) nephrogram when diatrizoate was used in selective nephroangiography (Fig. 1a).

The aim of the present investigation was to further evaluate postangiographic albuminuria and irregular nephrograms in an experimental model that allows simultaneous measurements of other parameters of renal function, such as renal blood flow, glomerular filtration rate (creatinine clearance), and diuresis. In dogs the effects of selective renal artery injections of saline and the osmotic diuretic mannitol were compared with the effects of injections of the commonly used ionic ratio 1.5 contrast medium diatrizoate.

Material and Methods

Eighteen mongrel dogs ranging in weight from 14 to 27 kg (median weight 19 kg) had free access to

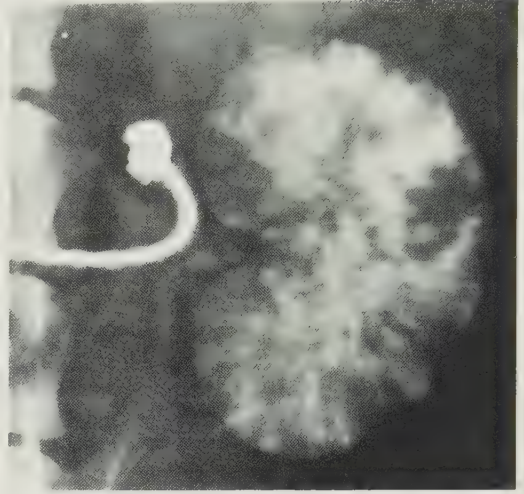
Accepted for publication 15 February 1984.

water and were fasted overnight before the experiments. They were anesthetized with an intravenous injection of 24 mg/kg body weight of pentobarbitone (Mebumal, ACO) and connected to a respirator by an endotracheal tube. The anesthesia was maintained throughout the experiments with an intravenous infusion of fentanyl (Leptanal, Leo) in a 5.5% glucose solution (100–200 ml solution/hour containing 0.1 mg fentanyl/100 ml); and, when needed, additional doses of pentobarbitone were given. The condition of the animals during the experiments was monitored by analyzing arterial blood gases and by recording pulse rate and blood pressure.

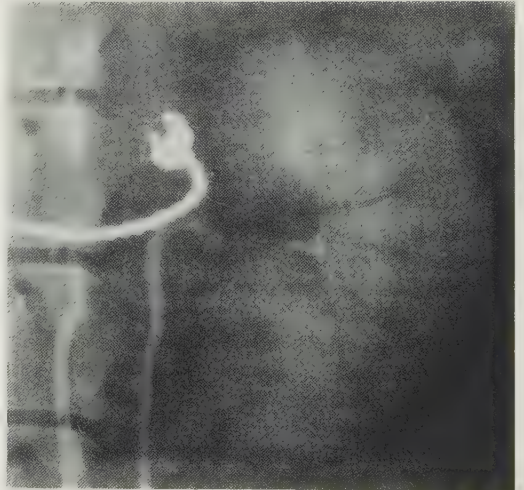
The experimental model is schematically illustrated in Fig. 2. After laparotomy by a median incision, a suitable flow probe was applied around the left renal artery for continuous mean volumetric blood flow recording with an electromagnetic flow meter (Nycotron, model 376) connected to a recorder (Mingograf, Siemens-Elema). For continuous urine flow recording and urine sampling, a catheter (PE 100, Clay Adams) was inserted into each ureter. Then, the abdominal incision was sutured and a polyethylene catheter (OD 2.2 mm, ID 1.45 mm, Mediplast) was inserted into each femoral artery. The left catheter was used for injecting the test solution into the left renal artery. The tip of the right catheter was placed in the abdominal aorta for pulse and blood pressure recording via a pressure transducer (EMT 34, Elema-Schönander) connected to the recorder.

The test solutions were saline (NaCl 9 mg/ml, ACO), mannitol (Mannitol 150 mg/ml, ACO), and the ionic contrast medium sodium/meglumine diatrizoate, w/w 10/66 (Urografin 76%, 370 mg iodine/ml, Schering AG). The number of dogs receiving each test solution and the osmolality and concentration of each test solution are given in Table 1. Each dog received three selective left renal artery injections of one of the test solutions at 15-min intervals dosed at 1 ml/kg body weight in each injection. The tip of the catheter was always proximal to the flow probe during the injection and each injection was given manually. The injection was administered as rapidly as possible (approximately 1 ml/s), but avoiding retrograde escape of the contrast medium into the aorta. Immediately after each injection the catheter tip was withdrawn to the aorta. No injection was given to the right kidney, which served as a control.

Injections of the contrast medium and the enhancement of the renal parenchyma with regard to



a



b

Fig. 1. a) Dog kidney with irregular (non-homogeneous) nephrogram ('patchy contrast medium retention') 15 min after three selective renal artery injections of diatrizoate 76% at 15-min intervals (1 ml/kg body weight in each injection). b) Dog kidney with homogeneous nephrogram 15 min after selective renal artery injections of diatrizoate 76% as described in legend to (a).

distribution and time, were monitored by fluoroscopy and recorded on videotape throughout the experiment. Special annotation was made of an irregular (non-homogeneous) nephrogram (Fig. 1a), here described as 'patchy contrast medium retention'.

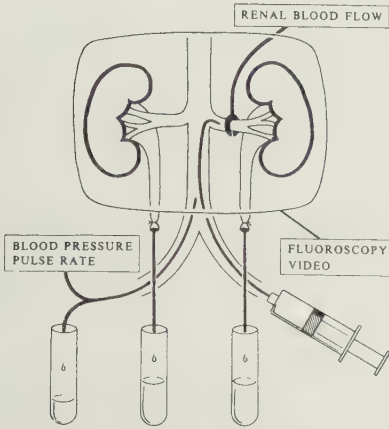


Fig. 2. The experimental model.

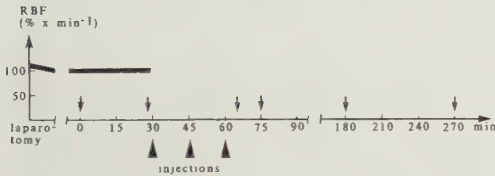


Fig. 3. The time schedule and the measurements of left renal artery blood flow (RBF). RBF was continuously measured, but for statistical calculations selected measurements were made as indicated by small arrows. After applying the flow probe and closing the abdominal incision, the RBF decreased 10 to 20 per cent for 15 to 20 min and then stabilized. Injections of test solution (large arrows) were not given until the RBF had been stable (fluctuation less than $\pm 10\%$) for 30 min. The beginning of this 30-min period was defined as time '0' on the abscissa and the RBF in this 30-min period was in each experiment assigned the value $100\% \times \text{min}^{-1}$. Postinjection RBF was expressed as a percentage of the preinjection RBF and was measured 5, 15, 120 and 210 min (small arrows) after the third injection of test solution. The time scale has been changed after 95 min.

Table 1

Number of dogs, test solutions, osmolality and concentration of the solutions

No. of dogs	Test solutions	Osmolality (mol/kg H ₂ O)	Concentration (mol/l)
7	Saline	0.28	0.16
3	Mannitol	0.95	0.82
8	Diatrizoate	2.1	0.97

Fig. 3 demonstrates the time schedule and the measurements of left renal artery blood flow (RBF) of each experiment.

Urine flow ($\text{ml} \times \text{min}^{-1}$) was calculated from

measurements of urine volumes from each kidney from time '0' (Fig. 3) every 15 min up to 90 min and then every 30 min up to 270 min (in Table 3 the diuresis is expressed in $\mu\text{l} \times \text{min}^{-1} \times \text{kg}$ body weight⁻¹). In urine samples collected from each kidney before injections (0–30 min, Fig. 3) and after the third injection (60–75 min, Fig. 3), the concentration of creatinine and albumin was determined using the Jaffé reaction and the radial immunodiffusion technique of MANCINI et coll. (16), respectively. The urinary albumin concentration was expressed per gram of urinary creatinine ($\text{g albumin} \times \text{g creatinine}^{-1}$), thereby relating albumin excretion to glomerular filtration rate. An arterial blood sample for creatinine analysis (Jaffé reaction) was drawn before injecting the test solution.

In the periods 0–30 min and 60–75 min (Fig. 3), creatinine clearance was calculated for each kidney according to the formula

$$Cl = \frac{V \times U}{P \times W}$$

Cl = creatinine clearance ($\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$)

V = urine flow ($\text{ml} \times \text{min}^{-1}$)

U = urinary creatinine ($\mu\text{mol} \times \text{l}^{-1}$)

P = serum creatinine ($\mu\text{mol} \times \text{l}^{-1}$)

W = body weight (kg)

Statistical evaluation was made according to Wilcoxon's test for paired observations or Mann-Whitney's rank sum test for unpaired data. A difference with a p-value of 0.05 or less was considered statistically significant.

Results

Renal blood flow (RBF). Following injections of saline the RBF was not significantly reduced when measured 5, 15, 120, and 210 min after the last injection (corresponding to 65, 75, 180, and 270 min in Fig. 4). The postinjection medians of RBF on each of these four occasions ranged between 84 and 96 per cent of preinjection RBF (Table 2, Fig. 4). The corresponding range of postinjection medians of RBF in the mannitol group was between 88 and 100 per cent. Following injections of diatrizoate (Table 2, complete diatrizoate group, $n=8$, and Fig. 4), the RBF was not significantly reduced when measured 5 and 15 min after the third injection, but 120 and 210 min later the RBF was significantly reduced

as compared with the preinjection RBF ($p < 0.01$) and was also significantly lower than the RBF following injections of saline ($p < 0.05$). The postinjection medians of RBF on each of the four measurement occasions ranged between 41 and 61 per cent in the complete diatrizoate group ($n=8$).

During the injections of diatrizoate, arterial spasm or occlusions of major renal arteries were not observed. Towards the end of the diatrizoate injections, the speed of the injections had to be decreased to avoid retrograde contrast medium flow into the aorta. During all diatrizoate injections there was an intense homogeneous accumulation of contrast medium in the left kidney. In five of eight dogs a patchy contrast medium retention in the renal parenchyma was seen a few minutes after the first injection following partial drainage of the contrast medium into the renal vein and pelvis. This irregularity of the nephrogram became more obvious after the subsequent injections and was observed 120 to 210 min after the last injection in four of these five dogs and for 30 min in the fifth (Fig. 1 a). In three dogs the dense and homogeneous nephrogram gradually disappeared without the occurrence of patchy contrast medium retention (Fig. 1 b). In all five dogs developing patchy contrast medium retention, the contrast medium injections produced a marked reduction in RBF. For these five dogs the postinjection medians of RBF on the four measurement occasions ranged between 16 and 57 per cent (Table 2, diatrizoate, $n=5$). This RBF was significantly lower than corresponding RBF following injections of saline (5 and 15 min postinjection: $p < 0.01$; 120 and 210 min postinjection: $p < 0.05$).

Fig. 5 shows the size of the postinjection RBF for each dog in the complete diatrizoate group 5 min after the last injection.

Albuminuria. There were no significant differences in preinjection urinary albumin concentrations between the left and the right kidneys or between the saline and diatrizoate group (Table 3). Injections of saline did not significantly affect the urinary albumin concentrations, whereas injections of diatrizoate increased the median urinary albumin concentration approximately 400 times from the injected kidneys ($p < 0.01$), but produced no significant albuminuria from the non-injected kidneys. Kidneys with patchy contrast medium retention had the same degree of postinjection albuminuria as injected kidneys without such retention (Fig. 5).

Macroscopic hematuria was observed in postin-

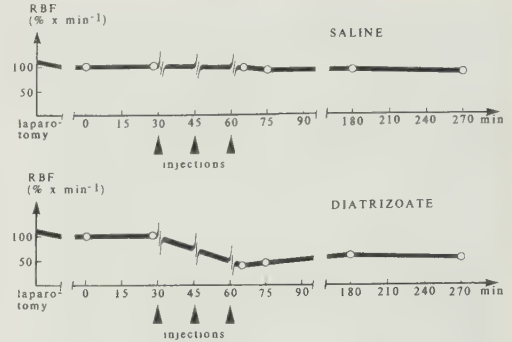


Fig. 4. Simplified graphs of left renal artery blood flow (RBF) following selective left renal artery injections of saline and diatrizoate. Median values have been used (Table 2; saline $n=7$, diatrizoate $n=8$). Each circle indicates time when RBF was measured. The time scale has been changed after 95 min.

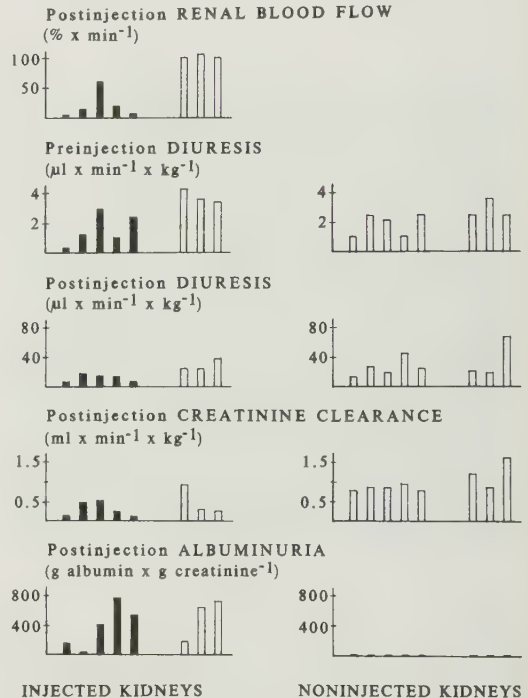


Fig. 5. Diagrams illustrating individual data from eight dogs injected with diatrizoate into left renal artery. Each column represents one kidney and injected kidneys are given in the left diagrams and corresponding control kidneys (non-injected) in the right diagrams. Black columns represent kidneys developing patchy contrast medium retention and white columns kidneys without such retention. The columns are based on data given in Tables 2 and 3. The postinjection renal blood flow (RBF) refers to measurements 5 min after the third diatrizoate injection. The scale for preinjection diuresis is 20 times larger than the scale for postinjection diuresis (i.e., all kidneys had a marked increase in diuresis following injections of diatrizoate).

Table 2

Renal blood flow (RBF) in the left renal artery after selective left renal artery injections of saline, mannitol or diatrizoate, calculated 5, 15, 120 and 210 min after the third injection (corresponding to 65, 75, 180 and 270 min in Fig. 3). Number of dogs in each group = n. Data on five dogs with patchy contrast medium retention are given in a subgroup of diatrizoate (n=5). All values as a percentage of preinjection RBF. Median and range in parentheses

	5 min postinj.	15 min postinj.	120 min postinj.	210 min postinj.
Saline (n=7)	96 (80–100)	90 (80–100)	88 (70–120)	84 (54–100)
Mannitol (n=3)	88 (88–113)	88 (80–94)	100 (94–109)	88 (83–113)
Diatrizoate (n=8)	41 (6–106)	44 (16–114)	61* (22–89)	55* (29–86)
Diatrizoate (n=5)	16*** (6–60)	19*** (16–24)	57* (22–89)	48* (29–86)

* $p < 0.05$; *** $p < 0.01$ compared with saline group.

Table 3

Pre- and postinjection values of albuminuria, creatinine clearance, and diuresis are given for injected and non-injected kidneys of dogs given saline, mannitol or diatrizoate into their left renal artery. The albuminuria is expressed in $\text{g albumin} \times \text{g creatinine}^{-1}$, creatinine clearance in $\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$ and the diuresis in $\mu\text{l} \times \text{min}^{-1} \times \text{kg}^{-1}$. The sampling periods are illustrated in Fig. 3. Number of dogs in each group = n. Median and range in parentheses

	Albuminuria		Creatinine clearance		Diuresis	
	Preinj. (0–30 min)	Postinj. (60–75 min)	Preinj. (0–30 min)	Postinj. (60–75 min)	Preinj. (0–30 min)	Postinj. (30–270 min)
Saline (n=7)						
Injected	0.34 (0.15–3.1)	0.43 (0.12–1.5)	0.70 (0.18–0.95)	0.68 (0.24–0.73)	2.2 (1.7–2.8)	2.7 (2.2–3.9)
Non-injected	0.29 (0.055–0.95)	0.21 (0.12–1.7)	0.64 (0.19–1.1)	0.63 (0.27–1.1)	2.4 (1.5–3.2)	2.7 (2.0–4.2)
Mannitol (n=3)						
Injected	0.53 (0.39–1.4)	0.94 (0.33–1.7)	0.96 (0.57–1.1)	1.5 (0.92–1.6)	2.4 (1.5–3.3)	16 (12–18)
Non-injected	0.35 (0.22–0.39)	0.40 (0.19–1.2)	0.97 (0.77–1.2)	0.94 (0.57–1.3)	1.9 (1.9–3.1)	7.9 (6.7–9.6)
Diatrizoate (n=8)						
Injected	0.93 (0.091–3.1)	380*** (16–830)	0.85 (0.25–1.2)	0.28* (0.11–0.92)	2.7 (1.0–4.3)	18* (8.3–41)
Non-injected	0.37 (0.030–3.4)	0.16 (0.060–0.63)	0.71 (0.29–1.6)	0.85 (0.74–1.6)	2.5 (0.97–3.7)	25 (15–75)
	*** $p < 0.01$ compared with preinj. values		* $p < 0.05$ compared with preinj. values		* $p < 0.05$ compared with non-inj. kidneys	

jection urine samples from five of eight kidneys injected with diatrizoate, including two of those not developing patchy contrast medium retention.

Creatinine clearance. There were no significant

differences in preinjection creatinine clearance between the left and the right kidneys or between the saline and the diatrizoate group (Table 3). Injections of saline did not significantly influence creatinine

clearance. Injections of diatrizoate reduced the median value of creatinine clearance to approximately one-third of the preinjection value ($p < 0.05$), whereas these injections did not significantly influence creatinine clearance of the non-injected kidneys (Table 3). The postinjection creatinine clearance for the five kidneys developing patchy contrast medium retention ranged between 15 and 61 per cent of the creatinine clearance of the non-injected kidneys. The corresponding range for the three kidneys without patchy contrast medium retention was between 17 and 77 per cent of the values of the non-injected kidneys (Fig. 5).

Diuresis. There were no significant differences in preinjection diuresis between the left and the right kidneys or between the saline and diatrizoate group (Table 3). In the saline group there was no significant increase in diuresis from any kidney after the injections, whereas in the mannitol group there was a sevenfold increase in the median diuresis from the injected kidneys and a fourfold increase from the non-injected kidneys. Finally, in the diatrizoate group ($n=8$) the median value of diuresis increased sevenfold for the injected kidneys and tenfold for the non-injected kidneys. The postinjection diuresis from the injected kidneys in this group was significantly lower than that from the non-injected kidneys ($p < 0.05$).

The preinjection diuresis for the five kidneys developing patchy contrast medium retention was lower than for those not developing such retention (Fig. 5). After injections of diatrizoate, these five kidneys and one of those that did not develop patchy contrast medium retention produced less urine than the non-injected kidneys ranging from 30 to 74 per cent of the diuresis of the non-injected kidneys. The two other injected kidneys not developing patchy contrast medium retention produced more urine than the non-injected kidneys: 110 and 130 per cent of the diuresis of the non-injected kidneys (Fig. 5).

There were no consistent changes in arterial blood gases, pulse rate, and blood pressure; these remained within normal limits throughout the experiments in all the dogs.

Discussion

In all five kidneys with patchy contrast medium retention following selective renal artery injections of diatrizoate, the following factors (conditions) were present (Fig. 5): 1) Low postinjection renal

blood flow (RBF), 2) low preinjection diuresis, 3) low postinjection diuresis, 4) albuminuria and 5) low postinjection creatinine clearance.

Irregular distribution and abnormal retention of the contrast medium in the renal parenchyma following selective nephroangiography with diprotrizoate, iodopyracet, acetrizoate, and diatrizoate have been described by HELANDER (7), MORRIS et coll. (17) and SHERWOOD et coll. (25). They suggested 'impeded circulation', 'vascular spasm' and 'structural occlusion of vessels' as possible etiologic factors involved in abnormal contrast medium retention, obviously assuming that patchy contrast medium retention was a sign of reduced renal blood flow. In our investigation arterial renal blood flow was measured, and all the dogs with patchy contrast medium retention had a marked reduction in renal blood flow. In the comprehensive investigation by HELANDER (7), the following summary was made: 'A pathologic angioneurographic effect was invariably attended by both functional disturbances and morphologically demonstrable injuries. Functional tests showed that glomeruli as well as tubules were damaged. The morphologically detectable injuries had the character of tubular nephrosis, but there was glomerular damage too.' Our results suggest a connection between the patchy contrast medium retention and the reduction in RBF, but they do not reveal the causal relation between them. Moreover, the five dogs with patchy contrast medium retention had the smallest preinjection diuresis (Fig. 5), and this might indicate that they were the least hydrated, which could be relevant for the development of patchy contrast medium retention. Dehydration is one of the risk factors of contrast medium-induced acute renal failure, although its role in the pathogenesis is not clearly understood (2, 6, 18).

Irregular postangiographic nephrograms have also been reported following temporary occlusion of the renal artery (20) and following hemorrhagic hypotension (15) and these authors suggested cortical ischemia as a causal factor.

Previous investigations with electromagnetic flow meters on effects of selective renal artery injections of contrast medium on RBF in dogs have dealt with short-term effects and have demonstrated a biphasic response with a short increase (less than 1 min) and then a longer decrease (less than 15 min) in RBF (3, 12, 13, 23, 24). These investigators used diatrizoate or iothalamate in doses ranging from 3 to 8 ml (870–2300 mg iodine). Our investigation, with re-

peated renal artery catheterizations, was designed to evaluate long-term effects on RBF and has demonstrated a prolonged reduction in RBF lasting throughout the experiment, i.e., 3.5 hours following the last injection. A possible explanation of this discrepancy compared with the previous investigations is the higher contrast medium dose used in the present investigation, i.e., approximately 3 to 8 times more at each injection; moreover, the dose was repeated twice. The present results also show a great variation in RBF responses to diatrizoate and this might indicate individual susceptibility to this medium. The smaller variation in RBF responses in the saline group (Table 2) indicates that the main cause of the variation in the diatrizoate group is not due to errors of measurement of RBF.

Besides patchy contrast medium retention and a marked reduction in renal blood flow, the other functional disturbances (factors 3–5) were observed in all diatrizoate-injected kidneys. As regards low postinjection diuresis (factor 3), this is based on the comparison with the osmotic diuresis produced by mannitol, which has less than half the osmolality of diatrizoate (Table 1). Mannitol produced twice as much urine from the injected kidneys compared with the non-injected ones, whereas diatrizoate produced a higher diuresis from the non-injected kidneys in six dogs and only slightly more urine from the injected kidneys in two dogs (Table 3, Fig. 5).

Albuminuria following selective injections of contrast medium is related to the chemical structure of the contrast medium rather than to its osmolality (10). In the evaluation of postangiographic albuminuria in man and dog, HOLTÅS and co-workers (8–11), KRÅKENES et coll. (14) and TEJLER et coll. (27) mainly used urine samples from the bladder, thus being unable to study the albuminuria from each kidney. The present results demonstrate that massive albuminuria is related to selective injections and that there was no albuminuria from the non-injected kidneys, which accords with results from two dogs investigated with ureter catheters (10). The albuminuria is a sign of increased permeability of the glomerular membrane (27). The origin of the macroscopic hematuria is unknown but this was observed only in urine samples from diatrizoate-injected kidneys.

Glomerular filtration rate (GFR) is well reflected by creatinine clearance, as this equals inulin clearance in dogs (26). In agreement with the present results, contrast medium-induced reduction in GFR

has been reported by MULLADAY et coll. (19) and KATZBERG et coll. (13) following selective renal artery injections of diatrizoate in dogs. RHEA et coll. (22) found severe azotemia, in some instances fatal, and extensive histologic alterations in the kidneys following selective renal artery injection of sodium iothalamate in dogs. Moreover, FORREST et coll. (4) and REED et coll. (21) have reported reductions in GFR following intravenous injections of diatrizoate in dogs and rats, respectively, and in the latter report there was also a reduction in RBF.

In summary, selective renal artery injections of high doses of diatrizoate interfere with several parameters of renal function. Although the pathogenetic mechanisms involved or the causal relations between the observations cannot be established, the following hypothesis about the mechanisms producing patchy contrast medium retention may be advanced. During the injections of diatrizoate, all the injected kidneys had an intense homogeneous accumulation of contrast medium in the renal parenchyma. Therefore, the subsequent patchy contrast medium retention implies regional differences in drainage of the contrast medium. An injected contrast medium may leave the kidney through the vessels or the tubules. Accordingly, patchy contrast medium retention may be due to: 1) vascular obstructions—irregularly distributed, or 2) tubular obstructions—irregularly distributed, or 3) a combination of both phenomena. Vascular obstructions—for example, caused by thrombosis—mean reduced plasma flow and consequently reduced glomerular filtration rate and urine flow. Tubular obstructions—for example, caused by precipitated proteins (1, 5, 18)—mean reduced urine flow and increased intratubular pressure, which counteracts glomerular filtration rate. Increased intratubular pressure may cause capillary compression reducing renal blood flow. Even in the absence of precipitates in the tubules, the two latter mechanisms might be relevant solely due to the increased intratubular pressure caused by the filtrated hyperosmolal contrast medium (13).

Conclusions

In the presented experimental model, the high-osmolal ionic ratio 1.5 contrast medium diatrizoate interferes with several parameters of renal function.

1) Further research is warranted to evaluate whether these effects can be reduced by low-osmolal ratio 3.0 contrast media.

- 2) Further investigation of contrast medium-induced vascular and tubular obstructions may elucidate the pathogenesis of patchy contrast medium retention in the kidney.

ACKNOWLEDGEMENTS

This investigation was supported by the Swedish Medical Research Council (project No. 3483). The expert technical assistance of Anita Burnett and Britt-Marie Lilja is gratefully acknowledged.

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IRREGULAR NEPHROGRAMS AND ACCUMULATION OF
PLATELETS IN THE KIDNEY FOLLOWING SELECTIVE
NEPHROANGIOGRAPHY IN DOGS

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Abstract

Selective renal artery injections of large single doses of the ionic contrast medium metrizoate produced an irregular nephrogram, "patchy contrast medium retention", in 14 of 16 dogs. The irregular nephrogram was associated with a transient accumulation of platelets and fibrinogen in the kidney and with microscopically demonstrable transient thrombi in afferent arterioles and glomerular capillary tufts. These effects were followed by tubular damage, which was demonstrated in four of six dogs examined 48 hours postinjection. Formation of thrombi were not demonstrated in six dogs given small single doses, which also produced homogeneous nephrograms. It is suggested that contrast medium-induced endothelial damage is a pathogenetic mechanism in the development of thrombi and patchy contrast medium retention.

Introduction

Irregular (non-homogeneous) nephrograms following selective nephroangiography with ionic contrast media have been described by HELANDER (6), MORRIS et coll. (12), and SHERWOOD et coll. (18), and they assumed that this phenomenon was a sign of reduced renal blood flow. Irregular postangiographic nephrograms have also been reported following hemorrhagic hypotension (8) and following temporary occlusion of the renal artery (14).

TÖRNQUIST et coll. (19) performed selective nephroangiography in dogs with large doses of an ionic ratio 1.5 medium (diatrizoate), that initially produced a homogeneous nephrogram, which subsequently changed into an irregular nephrogram in high frequency. This change was caused by drainage of contrast medium from some parts of the renal parenchyma and by retention of contrast medium in other parts. The phenomenon, described as "patchy contrast medium retention" (Fig. 1a),

was associated with a marked decrease in renal blood flow. It was postulated that patchy contrast medium retention might be caused by irregularly distributed vascular and/or tubular obstructions in the kidney.

The aim of the present investigation was to evaluate "vascular obstructions" as an etiologic factor in the development of patchy contrast medium retention. Therefore, intrarenal accumulation of Cr-51-labeled platelets and I-125-labeled fibrinogen was measured and changes in renal vessels were evaluated in the light microscope after selective renal artery injections of the ionic contrast medium metrizoate given in different doses to dogs. Moreover, the dose dependence of patchy contrast medium retention was evaluated.

Material and Methods

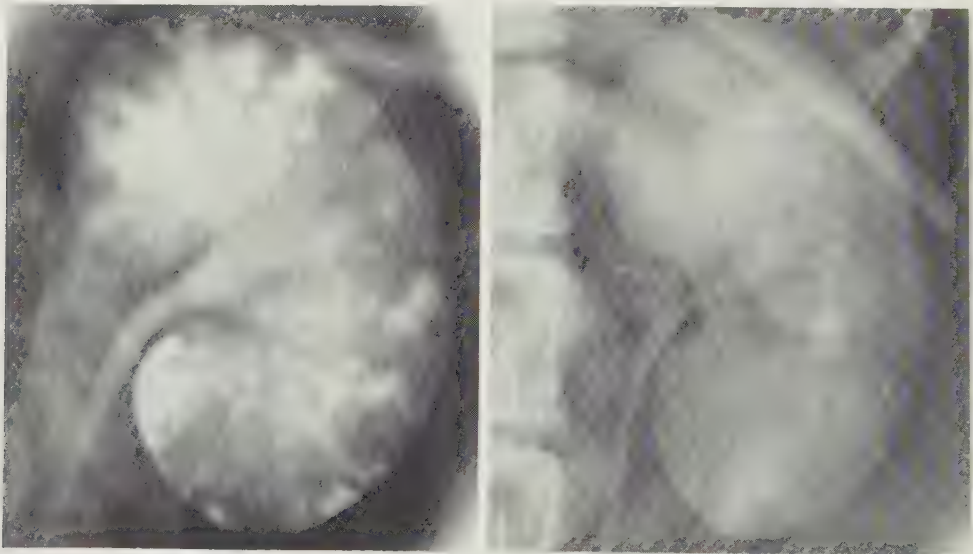
Twenty-two mongrel dogs of both sexes ranging in weight from 13 to 27 kg (median weight 19 kg) were splenectomized two to three weeks prior to nephroangiography. The day before nephroangiography, autologous platelets of all dogs were labeled in vitro with Cr-51 according to the technique of ABRAHAMSEN (1) as modified by LJUNGQVIST (10). In ten dogs allogenic fibrinogen, labeled in vitro with I-125 as described by McFARLANE (11) and modified by LEANDOER et coll. (9), was injected intravenously 2-5 days prior to nephroangiography.

The dogs were anesthetized with an intravenous injection of 25 mg/kg body weight of pentobarbitone (Nembutal Vet., ABBOT) and the anesthesia was maintained by additional doses (2.5-5 mg/kg b.w.) when needed. The dogs breathed spontaneously through an endotracheal tube and received an intravenous infusion of 100-200 ml/h of saline during the experiments.

Selective unilateral nephroangiography was performed via the right femoral artery with a polyethylene catheter (OD/ID

2.2/1.4 mm). The tip of the catheter remained in the renal artery for one hour, and during this period a varying number of injections of contrast medium were given. The injections and the contrast medium enhancement of the renal parenchyma were monitored by fluoroscopy continuing 15 min after the last contrast medium injection and at this time it was determined whether the nephrogram was homogeneous (Fig. 1b) or irregular (non-homogeneous); the latter is here called patchy contrast medium retention (Fig. 1a).

The ionic contrast medium sodium/calcium/meglumine metrizoate w/w/w 10/11/66 (Isopaque Coronar, 370 mg iodine/ml, Nyco A/S) was used for all the dogs. The total material of 22 dogs was divided into eight groups (Fig. 2) and in six of



a

b

Fig. 1a. Dog kidney with irregular (non-homogeneous) nephrogram ("patchy contrast medium retention") 15 min after five selective renal artery injections of 1 ml/kg body weight of metrizoate given every 12th minute during one hour (total dose 5 ml/kg b.w.). b) Dog kidney with homogeneous nephrogram 15 min after twenty selective renal artery injections of 0.5 ml/kg body weight of metrizoate given every third minute during one hour (total dose 10 ml/kg b.w.).

these groups the dogs were sacrificed one hour after the last contrast medium injection and in two groups after 48 hours for investigations of the kidneys. The size of each single injection is called "single dose" and the summation of all "single doses" given to one dog is called "total dose". The size of the "single doses" and the "total dose" used in each group is given in Fig. 2.

The number of injections varied between one and twenty in different dogs. When more than one injection was given, the injections were uniformly distributed within the "injection hour". The injections were administered as rapidly as possible, but avoiding retrograde escape of the contrast medium into the aorta. The non-injected kidney served as a control.

SINGLE DOSE ml/kg	TIME OF SACRIFICE AFTER CONTRAST MEDIUM INJECTION				
	1 HOUR			48 HOURS	
1.0-2.0	3	4	3	5	1
	(3)	(4)	(3)	(3)	(1)
0.2-0.5	1	3	2		
	(0)	(0)	(0)		
	2	5	10	2	5
	TOTAL DOSE ml/kg				

Fig. 2. The total material of 22 dogs was divided into eight different groups according to this figure. The dogs were injected with various single and total doses (ml/kg b.w.) of metrizoate into one renal artery during one hour. Sixteen dogs were sacrificed one hour after the last contrast medium injection and six dogs were sacrificed 48 hours postinjection for further investigations of the kidneys. Numbers within parentheses are numbers of dogs developing irregular nephrograms (patchy contrast medium retention) in the injected kidney. (In the text "large single doses" refer to 1.0-2.0 ml/kg b.w. whereas "small single doses" refer to 0.2-0.5 ml/kg b.w.).

Fourteen dogs received right renal artery injections and eight dogs left renal artery injections.

Sixteen dogs were sacrificed by intravenous pentobarbitone one hour after the last contrast medium injection and six dogs were sacrificed approximately 48 hours later. All the kidneys were removed and weighed. Each kidney was then divided into three parts of about equal size. The cranial and the caudal thirds of each kidney were homogenized and their Cr-51 and I-125 activities were determined in a NaI well crystal scintillation counter (Picker Autowell II) and expressed in counts per min per gram wet tissue. In each dog the ratio "Cr-51 activity in injected kidney/Cr-51 activity in non-injected kidney" was calculated and this ratio is here referred to as "relative platelet accumulation" (RPA). Analogously, "relative kidney weight" (RKW) and "relative fibrinogen accumulation" were calculated from kidney weights and I-125 activities, respectively.

In all the dogs the middle third of each kidney was fixed in 10 per cent formalin after bisection. The specimens were divided into 2-3 mm blocks, which were embedded in paraffin and cut into 5-micron sections. The stains used were: Hematoxylin-phloxine-saffron (H.P.S.), Periodic acid - Schiff's method (P.A.S.), Lendrum's Martius-scarlet-blue method (M.S.B.), and Periodic acid-silver-methenamine (P.A.S.M.). The histologic evaluation was performed blindly with special references to thrombi in the vessels.

Statistical evaluation was made according to Mann-Whitney's rank sum test for unpaired data and Fischer's exact probability test for independent samples. A difference with a p-value of 0.05 or less was considered statistically significant.

Results

Patchy contrast medium retention in the injected kidney was significantly more frequent ($p < 0.005$) in the 16 dogs that had received large single doses (1-2 ml/kg b.w.) of metrizoate (frequency 14/16 = 0.88) than in the six dogs that had received small single doses (0.2-0.5 ml/kg b.w.) (frequency 0/6 = 0.0) (Fig. 2).

There was no significant difference in frequency of patchy contrast medium retention between the five dogs that had received the largest total dose (10 ml/kg b.w.) (frequency 3/5 = 0.60) and the nine dogs that had received the smallest total dose (2 ml/kg b.w.) (frequency 6/9 = 0.67) (Fig. 2).

The relative platelet accumulation (RPA) and the relative kidney weight (RKW) when determined one hour postinjection were both significantly higher ($p < 0.01$) in the ten dogs that had received large single doses of the contrast medium and also had patchy contrast medium retention (RPA: median 8.1, range 2.3-15.5; RKW: median 1.30, range 1.06-1.47) than in the six dogs that had received small single doses of the contrast medium and also had homogeneous nephrograms (RPA: median 1.3, range 0.8-1.9; RKW: median 1.02, range 0.91-1.12) (Fig. 3).

The relative platelet accumulation and the relative kidney weight, when determined 48 hours postinjection in six dogs that had received large single doses of contrast medium, were both significantly lower ($p < 0.01$) (RPA: median 1.2, range 0.9-2.1, RKW: median 1.11, range 1.05-1.16) than in the ten dogs that also had received large single doses, but in which RPA and RKW were determined one hour postinjection (RPA: median 8.1, range 2.3-15.5, RKW: median 1.30, range 1.06-1.47) (Fig. 3).

The relative fibrinogen accumulation when determined one

hour postinjection in four dogs ranged between 2.1 and 4.1 in three dogs with patchy contrast medium retention, whereas one dog with a homogeneous nephrogram had the value 0.9. The relative fibrinogen accumulation, when determined 48 hours postinjection in six dogs ranged between 1.0 and 1.2 in five dogs, including three with patchy contrast medium retention, whereas the sixth had the value 2.2 (Fig. 3), and this dog had patchy contrast medium retention.

Microscopic examination of kidney specimens from dogs sacrificed one hour postinjection revealed no abnormalities in all 16 control kidneys and in all six kidneys injected with small single doses.

Thrombi in the renal vessels were found in specimens from all ten injected kidneys in the groups injected with large single doses and investigated one hour postinjection (Fig. 3). The distribution of the thrombi was irregular. Areas with thrombi were intermingled among areas with normal microscopic appearance. Thrombi were localized in the afferent arterioles and in the glomerular capillary tufts. In the kidneys with the highest values of relative platelet accumulation (12.1-15.5) in these groups, thrombi were found in the afferent arterioles and red blood cells were present in the vessel walls. The corresponding glomerular loops were completely obstructed by thrombi (Fig. 4a, b). Microscopically the thrombi appeared to consist mainly of platelets. Occasionally, formation of fibrin in association with the platelets could also be seen (Fig. 4c). In the kidneys with the lowest values of relative platelet accumulation (2.3-3.0) in these groups, platelet aggregates or only small scattered thrombi were found in the glomerular capillary tufts (Fig. 4d). In these specimens no thrombi were found in the afferent arterioles.

Microscopic examination of kidney specimens from dogs sacrificed 48 hours postinjection revealed no abnormalities in the specimens from the six control kidneys and from two of

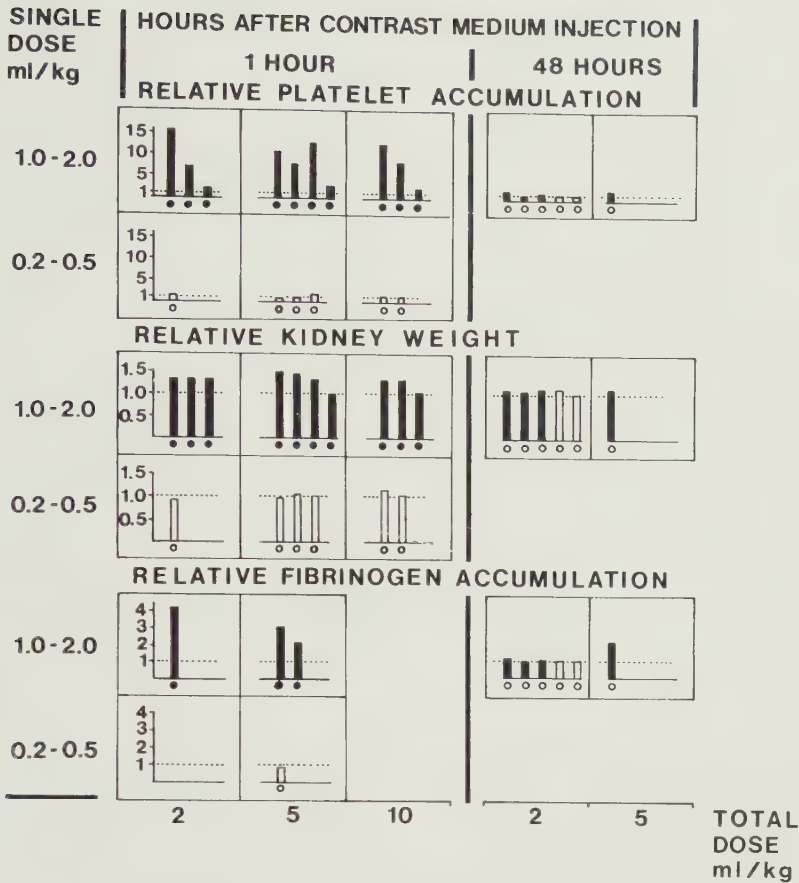


Fig. 3. This figure shows the parameters, which were determined following selective unilateral renal artery injections of various doses of metrizoate.

White columns represent injected kidneys with homogeneous nephrograms.

Black columns represent injected kidneys with patchy contrast medium retention.

The height of each column represents a ratio value in one dog, i.e.; ratio injected/non-injected kidney for Cr-51 activities, kidney weights, and I-125 activities here called relative platelet accumulation, relative kidney weight, and relative fibrinogen accumulation, respectively. Relative platelet accumulation and relative kidney weight were both determined one and 48 hours postinjection in 16 and 6 dogs, respectively. Relative fibrinogen accumulation was determined one and 48 hours postinjection in 4 and 6 dogs, respectively.

White circles represent injected kidneys without microscopically demonstrable thrombi.

Black circles represent injected kidneys with microscopically demonstrable thrombi.

Each dog is represented in the same position in the three different histograms.

the injected kidneys. Tubular changes were found in four of the injected kidneys, and the most pronounced abnormalities were present in the kidney with the highest value of relative fibrinogen accumulation. The areas with tubular lesions were irregularly distributed among areas with normal tubular epithelium. The degree of changes ranged from hydropic degeneration to cellular dissolution, with frank necrosis of the tubular epithelium. The tubules were frequently dilated and lined with flattened epithelium. Tubular casts composed of altered epithelial cells, red blood cells, and amorphous material, which might represent proteins, were frequently seen. The vessels in the areas with these tubular changes appeared normal and the glomeruli exhibited no evidence of damage.

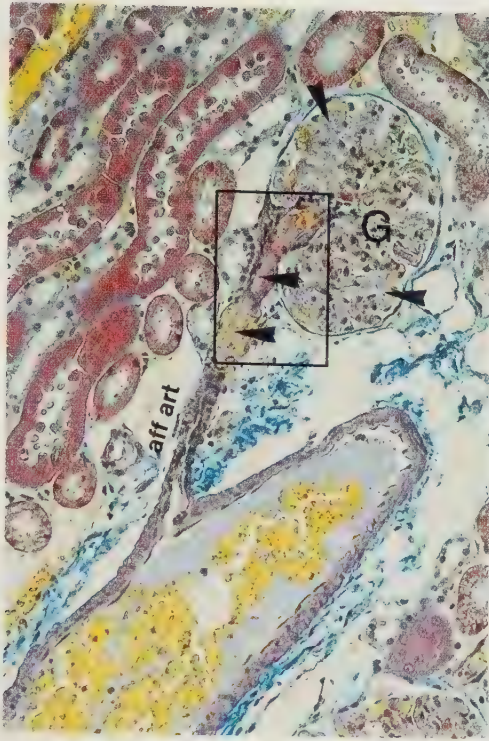
Fig. 4a. Specimen from dog kidney following ten selective renal artery injections of metrizoate (1 ml/kg b.w. in each injection). Platelet thrombi are completely obstructing the glomerular capillary loops and are also seen in the afferent arteriole (M.S.B. x 10).

b) Detail: red blood cells are seen in the vessel wall (M.S.B. x 40).

c) In another specimen from the same kidney fibrin is demonstrated in association with the platelet thrombi in the glomerular capillary loops (M.S.B. x 16).

d) Specimen from kidney following five selective renal artery injections of metrizoate (1 ml/kg b.w. in each injection). Small platelet thrombi are seen among normal capillary loops (P.A.S. x 16).

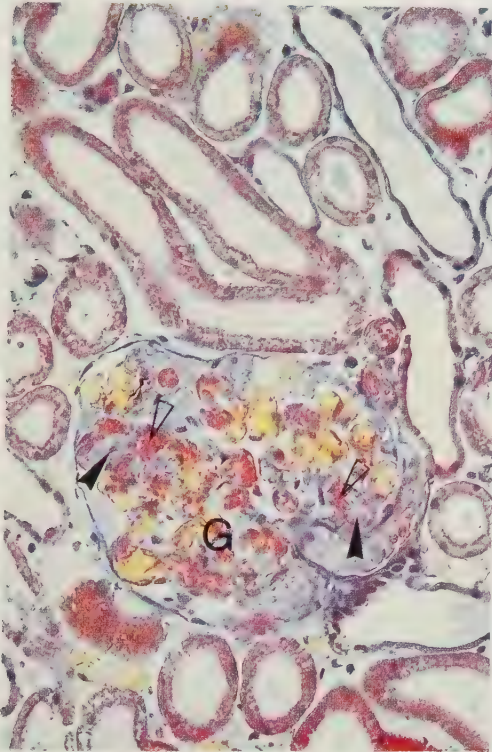
Glomerula (G), afferent arteriole (aff art), platelet thrombi (stained violet, arrowheads), red blood cells (stained yellow, arrows), fibrin (stained deep red, open arrowheads) and normal capillary loops (open arrows).



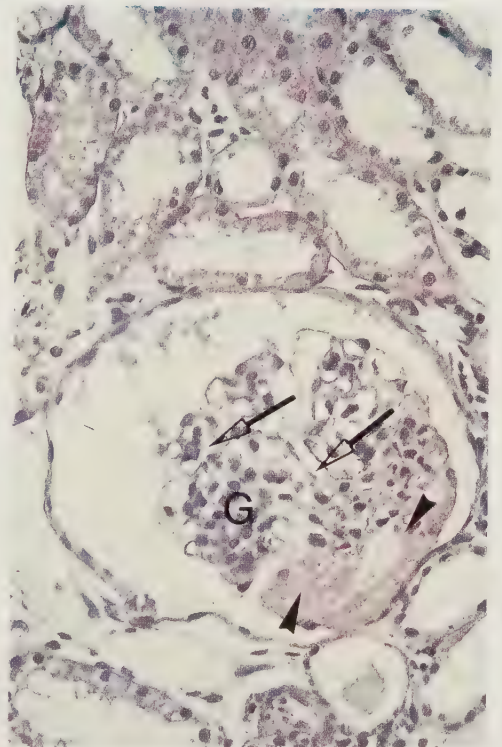
a



b



c



d

Discussion

In a previous report, five of eight dogs developed patchy contrast medium retention in the renal parenchyma following selective renal artery injections of diatrizoate (3 x 1 ml/kg b.w.; 370 mg I/ml). These five dogs also had a marked decrease in renal blood flow (19). The remaining three dogs had a homogeneous nephrogram and no marked reduction in renal blood flow. Since the patchy contrast medium retention suggested regional differences in drainage of the contrast medium, it was postulated that the phenomenon could be due to irregularly distributed vascular and/or tubular obstructions.

The results from the present investigation indicate that patchy contrast medium retention in the renal parenchyma is:

1. related to selective renal artery injections of large single doses of the contrast medium but not to a large total dose when injected as several small single doses;
2. associated with a transient accumulation of platelets in the kidney and possibly also with a transient accumulation of fibrinogen;
3. associated with a transient increase in kidney weight;
4. associated with microscopically demonstrable transient platelet aggregates and thrombi in glomerular capillary tufts and in afferent arterioles;
5. associated with tubular damage, which is demonstrable after the transient formation of thrombi.

Following transplantation of kidneys in dogs, endothelial cell damage and accumulation of platelets and fibrinogen have previously been observed in rejecting kidneys (3). Hyperosmolar contrast media may cause endothelial damage (13), and this injury may predispose to thrombus formation (2, 16). Adhesion of platelets to the vessel wall has been observed by in vivo microscopy of the bat wing following intraarterial injection of diatrizoate (21).

The present results may be interpreted as follows: Selective renal artery injections of large single doses of the hyperosmolar metrizoate cause damage to the vascular endothelium on which platelets and subsequently fibrinogen accumulate producing microscopically demonstrable thrombi. This interpretation is compatible with the previously demonstrated postangiographic reduction in renal blood flow (19), which could be caused not only by obstruction of the vessel lumen by the platelets but also by release of vasoactive substances, such as serotonin, from the platelets.

The increased kidney weight following renal artery injections of large single doses of the contrast medium is interpreted as fluid retention in the kidney. A part of this fluid retention is abnormally retained contrast medium, which is directly observed as the patchy contrast medium retention. Another part of the fluid retention might be edema caused by disturbances in the microcirculation of the injected kidneys.

The transient nature of these hemodynamic events is indicated by high values of relative platelet accumulation, relative fibrinogen accumulation, relative kidney weight and the presence of histologically demonstrable thrombi in kidneys examined one hour postinjection and by subsequent low values of these parameters and no histologically demonstrable thrombi in kidneys examined 48 hours postinjection. Regression of the vascular lesions might be due to thrombolytic mechanisms and restoration of renal blood flow.

The tubular damage found in specimens from injected kidneys examined 48 hours postinjection might be caused by a direct toxic effect of the contrast medium on the tubular epithelium and/or by effects from a locally reduced renal blood flow caused by obstructing thrombi. Such thrombi were found in kidneys examined one hour postinjection but not in kidneys examined 48 hours postinjection. These results also demonstrate a risk of misinterpreting the contrast medium effects.

If microscopic examination had only been performed one hour after the contrast medium injection merely vascular lesions (thrombi) would have been found, whereas if microscopic investigation had only been performed 48 hours postinjection no thrombi and merely tubular damage would have been found.

The relation between the doses of the the contrast medium and the demonstrated effects shows that the kidney may tolerate a large total dose of a hyperosmolar contrast medium administered as several small single doses without platelet aggregation and thrombus formation. On the other hand a much smaller total dose might induce thrombus formation when injected in one or a few large single doses. These results might be explained by a hypothesis that assumes that when the contrast medium concentration exceeds a certain value in the cell membrane and/or in the interior of endothelial cells these cells become damaged to such a degree that platelet adhesion and aggregation are induced on their surface as the first step in thrombus formation. For a damaging contrast medium concentration to arise, a certain period of contact is necessary between the contrast medium in the vessel lumen and the surface of the endothelial cells. Therefore, a large single dose (with a long period of contact) could lead to a damaging concentration, whereas small single doses (with short periods of contact) might not, because the contrast medium concentration in the cells might decrease between the injections when blood instead of contrast medium flows over them.

Recently, WEIBULL et coll. (20) reported reversible renal failure associated with abnormal retention of contrast medium, demonstrated by computed tomography, following percutaneous transluminal angioplasty in three patients. During this procedure, the renal vascular bed may be exposed to a hyperosmolar contrast medium in high concentration for periods of varying length when perfusion is completely obstructed by the inflated balloon catheter, and the total effect might be de-

leterious to the vascular endothelium.

Platelet accumulation and thrombus formation on intravascular catheters have been demonstrated in dogs (7) and represent a potential source of thromboembolism. However, platelet emboli from the catheters do not seem to be a major factor affecting the present results, because in all the dogs the catheter had been placed in a renal artery during a period of equal length and there were no signs of thrombi in the dogs receiving small single doses of the contrast medium.

Primary contrast medium-induced aggregation of the platelets in the general vascular bed associated with secondary trapping of the platelet aggregates in the kidney is not a plausible explanation of the present results, as there were no thrombi in the control kidneys.

Reports of contrast medium interaction with platelet function are contradictory and, contrary to the present investigation, most reports deal with in vitro experiments. Inhibition of platelet aggregation has been reported by ZIR et coll. (22), SHAPIRO et coll. (17), and COGAN et coll. (41) using aggregometers, whereas FRITZLER et coll. (5) found platelet aggregation by electron microscopy. Contrast medium-induced release of serotonin from platelets has been reported by RING & SOVAK (15), whereas ZIR et coll. (22) found inhibition of serotonin release.

Conclusions

1. Selective renal artery injection of large single doses of an ionic contrast medium may produce transient thrombi in the renal vascular bed.
2. Patchy contrast medium retention in the kidney suggests renal hemodynamic disturbances, which may be followed by tubular damage.
3. "Hemodynamic effects" and "tubular toxicity" are often considered as separate "mechanisms", when discussing the pathogenesis of contrast mediuminduced acute renal failure. Tubular damage may be secondary to hemodynamic changes.
4. In clinical nephroangiography the size of the single dose injected into a renal artery should be kept as small as possible to decrease the risk of formation of small thrombi.

ACKNOWLEDGEMENTS

This investigation was supported by the Swedish Medical Research Council (Projects No. 3483 and B85-17X-00759-20C). The skilful help of Christina Lindqvist M.T. is gratefully acknowledged.

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RENAL FUNCTION FOLLOWING NEPHROANGIOGRAPHY WITH
METRIZAMIDE AND IOHEXOL

Effects on renal blood flow, glomerular permeability
and filtration rate and diuresis in dogs

C. TÖRNQUIST, T. ALMÉN, K. GOLMAN and S. HOLTÅS

Abstract

The non-ionic ratio 3.0 contrast media metrizamide and iohexol used in high-dose unilateral nephroangiography in dogs produce homogeneous nephrograms and no marked effects on renal blood flow, glomerular filtration rate, and osmotic diuresis, in contrast to previously reported results using the same technique with iodine-equivalent doses of the ionic ratio 1.5 contrast medium diatrizoate (24). Iohexol affected glomerular permeability significantly less than metrizamide and diatrizoate.

Introduction

Intravascular administration of the commonly used ionic tri-iodinated ratio 1.5 contrast media (i.e., diatrizoate, iodamide, iothalamate, ioxithalamate and metrizoate) involves a risk of acute renal failure (6, 8, 14, 17). Thus, there is a need for contrast media with lower nephrotoxicity. To reduce the osmotic effects of contrast media (the osmolality of ratio 1.5 media is five to seven times that of human plasma in commonly used concentrations), the development of non-ionic ratio 3.0 contrast media was suggested (1). The lower osmolality of these compounds meant reduced osmotic effects but they also had a lower chemotoxicity than the ratio 1.5 media when compared in iodine-equivalent concentrations. The low chemotoxicity of the first non-ionic medium, metrizamide, was observed both as a low intravenous toxicity and as a low subarachnoid toxicity (20), which lead to its widespread use for myelography.

For intravascular use, metrizamide was found to have several advantages when compared with the ratio 1.5 media (3, 7). However, metrizamide was demonstrated to produce similar adverse effects on the kidney as the ratio 1.5 media, such as albuminuria following nephroangiography in man and dog (10,

11), osmotic nephrosis following urography in man (15), and increased mitotic rate in tubular cells following nephroangiography in rabbits (21).

Recently, an ionic ratio 3.0 contrast medium (ioxaglate) and two new non-ionic ratio 3.0 media (iopamidol and iohexol), have been introduced in clinical radiology. Experimental research and clinical trials have demonstrated that intravascular use of these media signifies advantages similar to those of metrizamide when compared with the ratio 1.5 media (4, 7, 13). Contrary to metrizamide, these new media tolerate autoclaving and are supplied as sterile solutions, which is of great practical and economic importance.

In a previous investigation in dogs, selective renal artery injections of the ionic ratio 1.5 contrast medium diatrizoate produced an irregular (non-homogeneous) nephrogram (Fig. 1a), a decrease in renal blood flow, massive albuminuria, and a decrease in glomerular filtration rate and a reduced osmotic diuresis (24). The aim of the present investigation was to determine if metrizamide and/or iohexol when used in that experimental model produced fewer signs of acute nephrotoxicity than diatrizoate.

Material and Methods

The details of the experimental design have previously been described (24).

Eighteen mongrel dogs ranging in weight from 13 to 30 kg (median weight 16 kg) were anesthetized with intravenous administration of pentobarbitone and fentanyl and connected to a respirator by an endotracheal tube. Following laparotomy, a flow probe was placed around the left renal artery for measurement of blood flow and a catheter was inserted into each ureter for urine sampling and measurement of diuresis. The

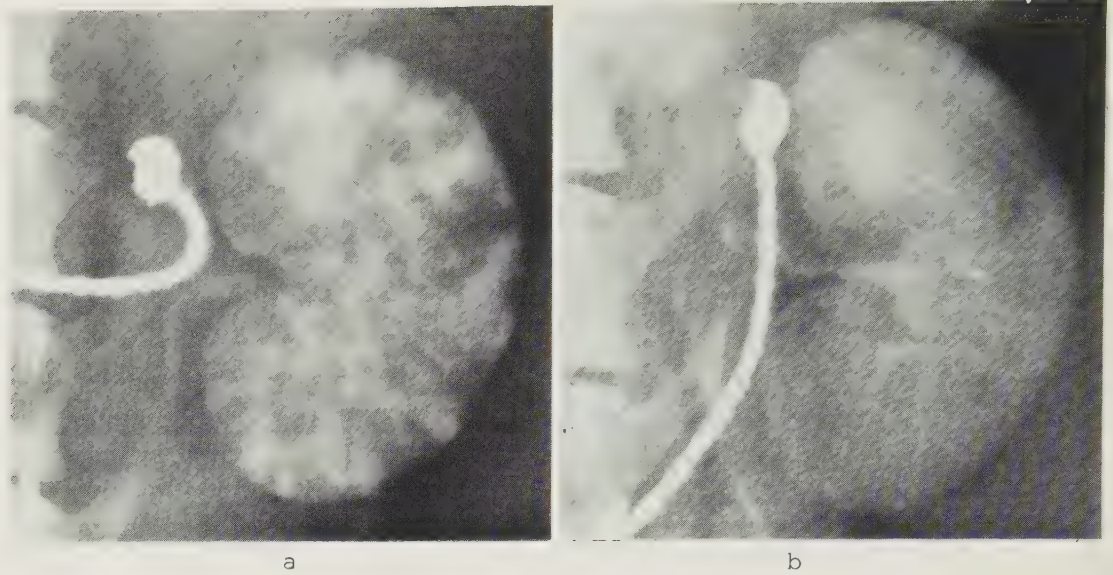


Fig. 1a) Dog kidney with irregular (non-homogeneous) nephrogram ("patchy contrast medium retention") 15 min after three selective renal artery injections of diatrizoate at 15-min intervals (370 mg iodine/kg body weight in each injection).
 b) Dog kidney with homogeneous nephrogram 15 min after three selective renal artery injections of iohexol at 15-min intervals (370 mg iodine/kg body weight in each injection).

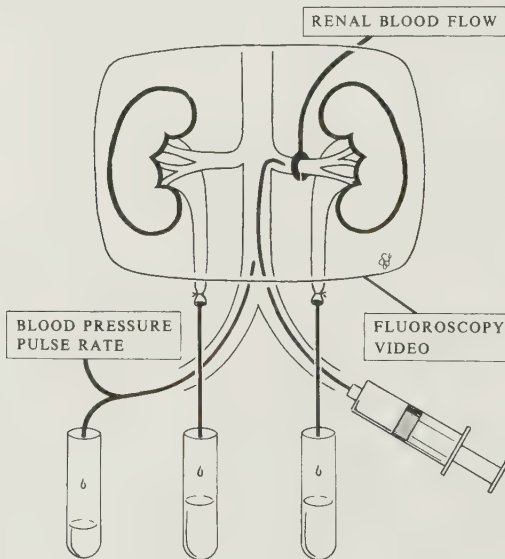


Fig. 2. The experimental model.

experimental model is schematically illustrated in Fig. 2. Nine dogs received three selective left renal artery injections of metrizamide (Amipaque, 370 mg iodine/ml, Nyegaard & Co A/S) and nine other dogs were similarly injected with io-hexol (Omnipaque, 370 mg iodine/ml, Nyegaard & Co A/S). The injections were given at 15-min intervals and dosed at 1 ml/kg body weight in each injection. No injection was given to the right kidney, which served as a control. The osmolality and concentration of each test solution are given in Table 1, which also includes data from two groups of dogs injected with diatrizoate and saline in a previous investigation (24), in which the experimental model was the same as in the present investigation.

The condition of the animals during the experiments was monitored by analyzing arterial blood gases and by recording pulse rate and blood pressure.

The following parameters were studied:

1. Mean volumetric blood flow in the left renal artery (RBF) was continuously measured by an electromagnetic flow meter throughout each experiment. Fig. 3 demonstrates the time

Table 1. Number of dogs, test solutions, osmolality and concentration of the solutions. Data from the previous report (24) on the two groups injected with diatrizoate and saline are also given

Number of dogs	Test solutions	Osmolality mol/kg H ₂ O	Concentration	
			mol/l	mg I/ml
9	Metrizamide	0.58	0.97	370
9	Iohexol	0.98	0.97	370
8	Diatrizoate	2.1	0.97	370
7	Saline	0.28	0.16	-

schedule and the measurements of RBF of each experiment. Two dogs in the metrizamide group and one in the iohexol group were excluded from the RBF calculations because of a technical fault in the RBF recorder.

2. Injections of the contrast media and enhancement of the renal parenchyma, with regard to distribution and time (the nephrogram), were monitored by fluoroscopy and recorded on videotape throughout the experiments. The nephrograms were evaluated as homogeneous (Fig. 1b) or irregular (non-homogeneous; Fig. 1a).

These irregular nephrograms arose from an initially homogeneous nephrogram and they are therefore referred to as "patchy contrast medium retention" (details of the development of the nephrograms are given in the results).

3. The albumin concentration was measured in the urine collected from each kidney during a 30-min period before the first (0-30 min, Fig. 3) and during a 15-min period after the third contrast medium injection (60-75 min, Fig. 3). In the iohexol group the albumin concentration was also determined in urine collected during a 30-min period at the end of the experiment (240-270 min, Fig. 3). The urinary albumin concentration was expressed per gram of urinary creatinine ($\text{g albumin} \times \text{g creatinine}^{-1}$), thereby relating albumin excretion to glomerular filtration rate.

4. Creatinine clearance ($\text{ml} \times \text{min}^{-1} \times \text{kg body weight}^{-1}$) for each kidney was calculated from measurements of the urine flow and urinary creatinine in the urine collected during the 30-min period before the first (0-30 min, Fig. 3) and during the 15-min period immediately after the third contrast medium injection (60-75 min, Fig. 3) and from measurement of serum creatinine in a blood sample drawn before injections of test solutions. In the iohexol group creatinine clearance for each kidney was also calculated for the 30-min period at the end

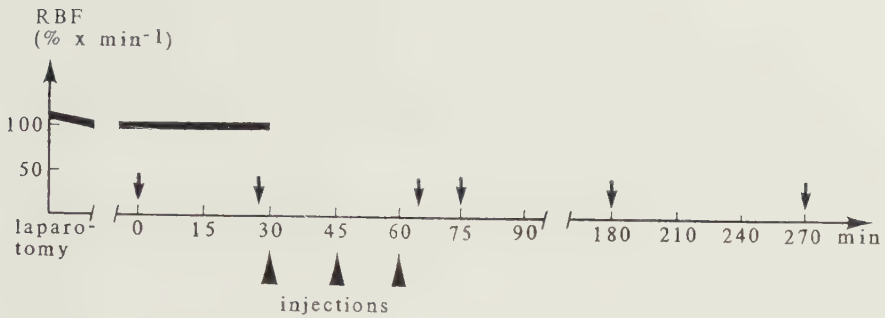


Fig. 3. The time schedule and the measurements of left renal artery blood flow (RBF). RBF was continuously measured, but for statistical calculations selected measurements were made as indicated by small arrows. After applying the flow probe and closing the abdominal incision, the RBF decreased 10 to 20 per cent for 15 to 20 min and then stabilized. Injections of test solution (large arrows) were not given until the RBF had been stable (fluctuation less than $\pm 10\%$) for 30 min. The beginning of this 30-min period was defined as time "0" on the abscissa and the RBF in this 30-min period was in each experiment assigned the value $100\% \times \text{min}^{-1}$. Postinjection RBF was expressed as a percentage of the preinjection RBF and was measured 5, 15, 120 and 210 min (small arrows) after the third injection of test solution. The time scale has been changed after 95 min.

of the experiment (240-270 min, Fig. 3) by corresponding measurements for that period.

5. The diuresis ($\mu\text{l} \times \text{min}^{-1} \times \text{kg body weight}^{-1}$) was calculated from measurements of urine volumes produced by each kidney during every 15-min period up to 90 min and then during every 30-min period up to 270 min (Fig. 3).

Statistical evaluation was made according to Wilcoxon's test for paired observations or Mann-Whitney's rank sum test for unpaired data. A difference with a p-value of 0.05 or less was considered statistically significant.

Results

The results are given in Tables 2 and 3 and Fig. 4, which include the results from the previous report on the two groups injected with diatrizoate and saline (24). The term significant means statistical significance.

Renal blood flow (RBF). Following injections of metrizamide, iohexol, and saline, RBF was not significantly reduced when measured 5, 15, 120, and 210 min after the last injection (Table 2 and in Fig. 4 corresponding to 65, 75, 180, and 270 min). Following injections of diatrizoate (Table 2, complete diatrizoate group, $n=8$ and Fig. 4), the RBF was not significantly reduced when measured 5 and 15 min after the third injection, but 120 and 210 min after this injection the RBF was significantly reduced as compared with the preinjection RBF ($p<0.01$). Postinjection RBF did not differ significantly between the metrizamide, iohexol, and saline groups. Postinjection RBF in the diatrizoate group (Table 2; complete diatrizoate group; $n=8$) did not differ significantly from the other groups 5 and 15 min after the third injection, but was significantly lower 120 and 210 min postinjection compared with the iohexol and saline group (diatrizoate-iohexol; 120 min: $p<0.01$; 210 min: $p<0.02$; diatrizoate-saline; 120 and 210 min: $p<0.05$), but did not differ significantly from the RBF in the metrizamide group.

During the injections of metrizamide, iohexol, and diatrizoate, arterial spasm or occlusion of major renal arteries were not observed. Towards the end of each injection, the speed of injection had to be decreased to avoid retrograde contrast medium flow into the aorta. During the injections of metrizamide and iohexol, there was an intense homogeneous accumulation of the contrast medium in the parenchyma of the left kidneys, and then it gradually decreased without the occurrence of patchy contrast medium retention in any single dog (Fig. 1b). Injections of diatrizoate also produced an in-

tense homogeneous accumulation of the contrast medium in the left kidney, but a few minutes after the first injection a patchy contrast medium retention in the renal parenchyma (Fig. 1a) was seen in five of eight dogs. During the subsequent injections there was again an intense homogeneous accumulation of the contrast medium in the renal parenchyma and a few minutes later an even more irregular nephrogram was observed (i.e., the size of the "patches" of contrast medium and in some instances the number of "patches" had increased). These five dogs also had a marked decrease in RBF (Table 2; diatrizoate, n=5). Postinjection RBF in these five dogs with patchy contrast medium retention was significantly lower at

Table 2. Renal blood flow (RBF) in the left renal artery after selective left renal artery injections of metrizamide and iohexol, calculated 5, 15, 120, and 210 min after the third injection (corresponding to 65, 75, 180, and 270 min in Fig. 4). Number of dogs in each group = n. Data from the previous report (24) on dogs selectively injected with diatrizoate (complete group: n=8; a subgroup of dogs with patchy contrast medium retention: n=5) and saline are also given. All values as a percentage of preinjection RBF. Median and range in parentheses

	5 min postinj.	15 min postinj.	120 min postinj.	210 min postinj.
Metrizamide (n=7)	83 (56-103)	88 (63-103)	88 (56-120)	67 (52-124)
Iohexol (n=8)	93 (25-133)	96 (25-122)	100 (72-107)	84 (64-100)
Diatrizoate (n=8)	41 (6-106)	44 (16-114)	61* (22-89)	55* (29-86)
Diatrizoate (n=5)	16*** (6-60)	19*** (16-24)	57* (22-89)	48* (29-86)
Saline (n=7)	96 (80-100)	90 (80-100)	88 (70-120)	84 (54-100)

* $p < 0.05$; *** $p < 0.01$ compared with saline group

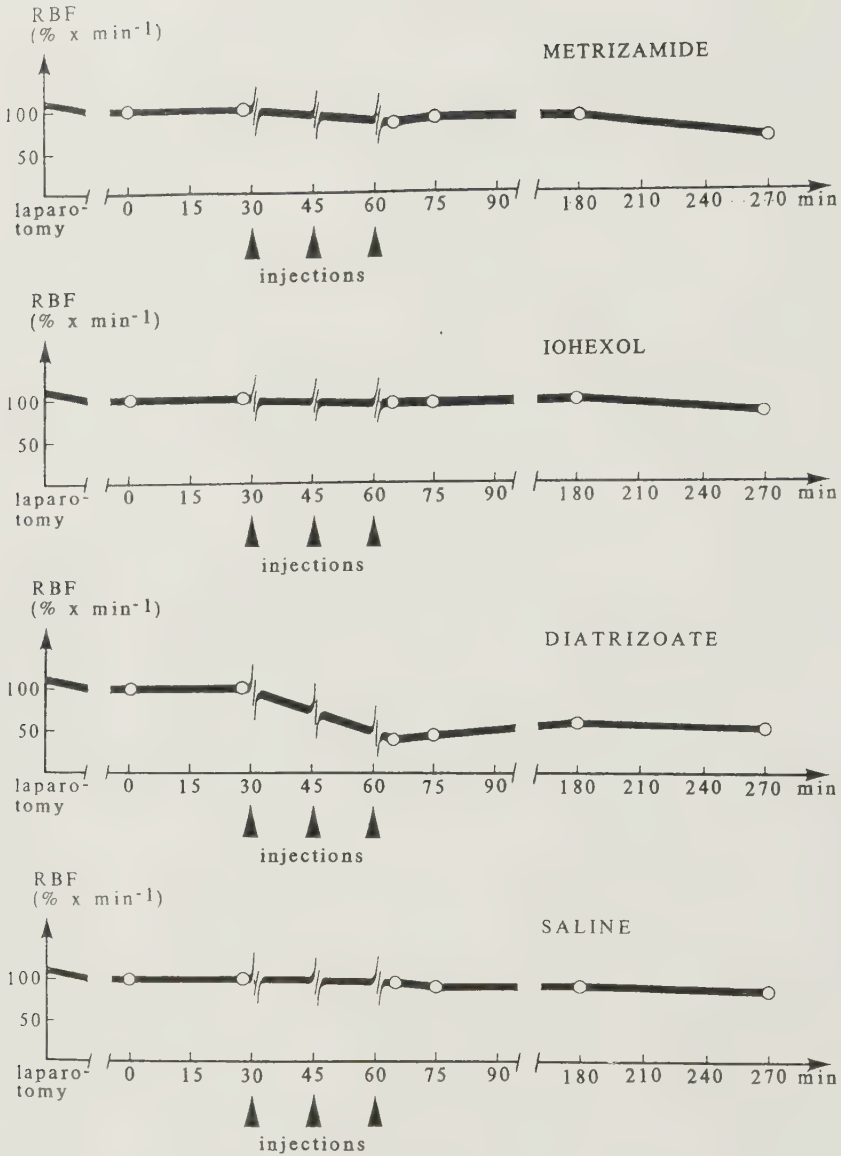


Fig. 4. Simplified graphs of left renal artery blood flow (RBF) following selective left renal artery injections of metrizamide, iohexol, diatrizoate and saline. Median values have been used (Table 2; diatrizoate $n=8$). Each circle indicates time when RBF was measured. The time scale has been changed after 95 min.

each of the four postinjection measurements than in the saline (Table 2) and iohexol groups (5 and 15 min postinj.: $p<0.01$; 120 min postinj.: $p<0.02$; 210 min postinj.: $p<0.05$). When compared with the metrizamide group, the dogs with patchy contrast medium retention had a significantly lower RBF 5 and 15 min postinjection ($p<0.01$), but 120 and 210 min postinjection there was no significant difference ($0.05<p<0.1$). Three diatrizoate-injected dogs had homogeneous nephrograms and no marked effects on renal blood flow.

Albuminuria. There were no significant differences in preinjection urinary albumin concentrations between the left and the right kidneys in the metrizamide, diatrizoate, and saline groups or between these groups (Table 3). In the io-hexol group the preinjection urinary albumin concentrations for the right kidneys were significantly lower than for the left kidneys ($p<0.05$). The preinjection urinary albumin concentrations for the left kidneys in the iohexol group did not differ significantly from the preinjection values for the left kidneys in the other three groups. Injections of metrizamide increased the median urinary albumin concentration from the injected kidneys approximately 1600 times, whereas io-hexol produced a 33-fold increase. Injections of diatrizoate increased the median urinary albumin concentration approximately 400 times. There was no significant increase in urinary albumin concentration from the non-injected kidneys in any group or from saline-injected kidneys.

The urinary albumin concentration in the samples drawn at the end of the experiment (240-270 min, Fig. 3) in the io-hexol group (these data are not given in Table 3) did not differ significantly from the preinjection values. The albuminuria produced by iohexol was significantly lower than the albuminuria produced by metrizamide ($p<0.01$) and diatrizoate ($p<0.05$). The albuminuria produced by metrizamide and diatrizoate did not differ significantly.

Macroscopic hematuria was observed in postinjection urine samples from five of nine kidneys injected with metrizamide, from one of nine kidneys injected with iohexol, and from five of eight kidneys injected with diatrizoate.

Creatinine clearance. There were no significant differences in preinjection creatinine clearance between the left and the right kidneys in any group or between the groups (Table 3). Injections of metrizamide, iohexol, and saline did not significantly influence creatinine clearance. Injections of diatrizoate reduced the median value of creatinine clearance of the injected kidneys to approximately one-third of the preinjection value ($p < 0.05$), whereas these injections did not significantly influence creatinine clearance of the non-injected kidneys.

Diuresis. There were no significant differences in preinjection diuresis between the left and the right kidneys or between the groups (Table 3). Injections of metrizamide increased the median diuresis fivefold from the injected kidneys and threefold from the non-injected ones. Injections of iohexol increased the median diuresis ninefold from the injected kidneys and fivefold from the non-injected ones. Injections of diatrizoate increased the median diuresis sevenfold from the injected kidneys and tenfold from the non-injected ones. Injections of metrizamide and iohexol produced a significantly higher diuresis from the injected kidneys compared with the non-injected ones, whereas diatrizoate induced a significantly lower diuresis from the injected kidneys compared with the non-injected ones (Table 3). Saline did not produce any significant changes in diuresis.

There were no consistent changes in arterial blood gases, pulse rate, and blood pressure; these remained within normal limits throughout the experiments in all the dogs.

Table 3

Pre- and postinjection values of albuminuria, creatinine clearance, and diuresis are given for injected (left) and non-injected (right) kidneys of dogs given metrizamide and iohexol into their left renal artery. Data from the previous report (24) on the groups injected with diatrizoate and saline are also given. The albuminuria is expressed in $\mu\text{l} \times \text{min}^{-1} \times \text{kg}^{-1}$, creatinine clearance in $\text{ml} \times \text{min}^{-1} \times \text{kg}^{-1}$, and the diuresis in $\mu\text{l} \times \text{min}^{-1} \times \text{kg}^{-1}$. The sampling periods are illustrated in Fig. 3. Number of dogs in each group = n. Median and range in parentheses

		Albuminuria		Creatinine clearance		Diuresis	
		Preinj. (0-30 min)	Postinj. (60-75 min)	Preinj. (0-30 min)	Postinj. (60-75 min)	Preinj. (0-30 min)	Postinj. (30-270 min)
Metrizamide (n=9)	Injected	0.31 (0.13-1.3)	510*** (25-1000)	0.52 (0.31-1.6)	0.68 (0.34-0.94)	3.0 (1.0-5.3)	16* (9.2-27)
	Non-injected	0.36 (0.027-1.8)	0.71 (0.10-1.7)	0.65 (0.34-1.4)	0.89 (0.51-1.4)	3.2 (1.3-6.0)	10 (6.3-13)
Iohexol (n=9)	Injected	0.72 (0.13-3.5)	24** (0.94-76)	0.75 (0.43-1.0)	0.76 (0.19-1.2)	1.9 (1.3-9.3)	17*** (12-30)
	Non-injected	0.46 (0.10-0.53)	0.39 (0.070-4.9)	0.79 (0.55-1.6)	0.94 (0.24-1.4)	1.9 (1.2-12)	10 (7.9-28)
Diatrizoate (n=8)	Injected	0.93 (0.091-3.1)	380*** (16-830)	0.85 (0.25-1.2)	0.28* (0.11-0.92)	2.7 (1.0-4.3)	18* (8.3-41)
	Non-injected	0.37 (0.030-3.4)	0.16 (0.060-0.63)	0.71 (0.29-1.6)	0.85 (0.74-1.6)	2.5 (0.97-3.7)	25 (15-75)
Saline (n=7)	Injected	0.34 (0.15-3.1)	0.43 (0.12-1.5)	0.70 (0.18-0.95)	0.68 (0.24-0.73)	2.2 (1.7-2.8)	2.7 (2.2-3.9)
	Non-injected	0.29 (0.055-0.95)	0.21 (0.12-1.7)	0.64 (0.19-1.1)	0.63 (0.27-1.1)	2.4 (1.5-3.2)	2.7 (2.0-4.2)

p<0.02; *p<0.01 compared with preinj. values

*p<0.05 compared with preinj. values

*p<0.05; ***p<0.01 compared with noninj. kidneys

Discussion

Selective renal artery injections of large doses of diatrizoate produced patchy contrast medium retention and a marked decrease in renal blood flow in five of eight dogs (24). Almén et coll. (2) found a high frequency of patchy contrast medium retention at similar dose-levels using metrizoate for selective renal artery injections in dogs and demonstrated that the phenomenon was related to the size of the single dose of the contrast medium, but not to a large total dose, when injected in several small single doses. Moreover, they found that patchy contrast medium retention was associated with accumulation of platelets and fibrinogen in the kidney, increased kidney weight, and microscopically demonstrable thrombi in the renal vascular bed.

Thus, selective renal artery injections of large single doses of ratio 1.5 contrast media in dogs produce effects indicating disturbances in renal hemodynamics. The homogeneous nephrograms produced by iodine-equivalent doses of the ratio 3.0 contrast media metrizamide and iohexol and the lack of marked effects on renal blood flow, demonstrated in the present investigation, show that these media interfere less with renal hemodynamics than ratio 1.5 media. In agreement with the present results, Morris et coll. (16), using an electromagnetic flowmeter on the renal artery, found less hemodynamic effect of metrizamide when compared with diatrizoate in nephroangiography in dogs.

Hyperosmolar ratio 1.5 contrast media may cause endothelial damage (18), and this injury may predispose to thrombus formation (5, 19). Almén et coll. (2) suggested that the metrizoate-induced accumulation of platelets and fibrinogen in the kidney and the microscopically demonstrable thrombi in the renal vascular bed in their investigation could be due to such contrast medium-induced endothelial damage and a secondary formation of microthrombi on that endothelium. Such mi-

crothrombi might also explain the reduction in renal blood flow, which was demonstrated in five of eight diatrizoate-injected kidneys (24). It has been shown that metrizamide and iohexol produce less endothelial damage than the ratio 1.5 media (18). This difference may imply a reduced risk of formation of microthrombi following injections of metrizamide and iohexol and may explain the homogeneous nephrograms and the lack of marked effects on renal blood flow produced by metrizamide and iohexol on the one hand and the patchy contrast medium retention and the marked reduction in renal blood flow produced by diatrizoate on the other.

Postangiographic albuminuria is a sign of increased permeability of the glomerular membrane (22), but its role in the etiology of contrast medium-induced acute renal failure is not known. The albuminuria is related to the chemical structure of the contrast medium rather than to its osmolality (9). This accords with the present results, demonstrating that iohexol produced significantly less albuminuria than metrizamide (which has a lower osmolality than iohexol) and diatrizoate (which has a higher osmolality than iohexol) (Table 1). In a previous investigation in dogs in which urine samples from the bladder were analyzed, selective renal artery injection of iohexol also produced significantly less albuminuria than diatrizoate (23). The present results demonstrate that postangiographic albuminuria is caused by selective injections of the contrast medium, as there was no albuminuria from the non-injected kidneys. Metrizamide and diatrizoate also produce albuminuria in clinical nephroangiography (10, 12), whereas iohexol does not (25).

Macroscopic hematuria was observed frequently in urine samples from diatrizoate- and metrizamide-injected kidneys. Although the origin of the hematuria is unknown, it is related to selective injections of the contrast media, as there was no macroscopic hematuria from the non-injected kidneys or from saline-injected kidneys.

Metrizamide and iohexol did not significantly affect glomerular filtration rate (GFR) as measured by creatinine clearance, whereas diatrizoate reduced the median value to one-third of the preinjection value in the injected kidneys. SKALPE & EVENSEN (21) used serum creatinine as an expression of GFR in nephroangiography in rabbits and found a slight, but statistically significant, increase in serum creatinine following injections of metrizoate but not following injections of metrizamide, which accords with the present results. TÖRNQUIST & HOLTÅS (25) also reported a slight, but statistically significant, increase in serum creatinine following nephroangiography with metrizoate in humans, whereas iohexol did not produce any increase in serum creatinine.

Selective renal artery injections of metrizamide and iohexol produced an osmotic diuresis with significantly higher urine production from the injected kidneys than from the non-injected ones. A similar osmotic diuresis was produced by selective renal artery injections of the osmotic diuretic mannitol in three dogs (24). Diatrizoate, on the other hand, induced a significantly lower urine production from the injected kidneys than from the non-injected ones. This diatrizoate-induced dysfunction of the injected kidneys, as well as the diatrizoate-induced decrease in glomerular filtration rate in the injected kidneys, could be secondary to the decrease in renal blood flow, which implies a reduced plasma flow, as both the filtration rate and the diuresis are dependent on the plasma flow.

Conclusion

The results from the present investigation suggest that the nephrotoxicity of iohexol is less than that of diatrizoate and metrizamide when used for nephroangiography in large doses. The future use of iohexol in humans will show whether this signifies a reduced risk of contrast medium-induced acute renal failure.

ACKNOWLEDGEMENTS

This investigation was supported by the Swedish Medical Research Council (project No. 3483). The expert technical assistance of Anita Burnett and Britt-Marie Lilja is gratefully acknowledged. We would like to thank Associate Professors Bertil Nosslin and Ulf Nyman for valuable advice and discussions.

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Renal Angiography with Iohexol and Metrizoate¹

The nephrotoxicity of the ionic contrast medium metrizoate was compared with that of nonionic iohexol when used for renal angiography. Fifteen patients who underwent renal angiography with metrizoate and 15 with iohexol were studied. Serum creatinine level, Cr-51-EDTA clearance, and urine albumin level were recorded before and after angiography. Metrizoate affected renal function, as indicated both by a transient decrease in glomerular filtration rate and by a transient albuminuria. Renal function was unaffected by iohexol. Furthermore, iohexol produced less subjective discomfort than metrizoate. There appeared to be no difference in the quality of the angiograms obtained with the two media.

Index terms: Contrast media, comparative studies • Contrast media, toxicity • Iohexol

Radiology 1984; 150: 331-334

THE INCREASING number of reports on contrast medium-induced acute renal failure caused by the commonly used triiodinated ionic media (1) is creating a growing interest in the nephrotoxicity of new contrast media.

The commonly used triiodinated ionic media (diatrizoate, iodamide, iothalamate, metrizoate) have a high osmolality in relation to their iodine content. Solutions of these media contain two particles (ions) per three iodine atoms and are therefore referred to as ratio 1.5 media (number of iodine atoms/number of particles). To increase the patient's tolerance for contrast media, one approach is to reduce the osmotic effects of the contrast media (2) by reducing their osmolality in relation to their iodine content, which is achieved by increasing the iodine/particle ratio.

The introduction of metrizamide, the first nonionic monomeric iodinated ratio 3.0 contrast medium in clinical use, was a milestone in diagnostic radiology. In the neuroradiological field, metrizamide, when introduced into the subarachnoid space, has a much lower toxicity than other water-soluble contrast media; in vascular studies, metrizamide has many advantages compared with the commonly used ionic media (2-3). However, most investigators have found that the nephrotoxicity of metrizamide is approximately the same as that of the ratio 1.5 media (3-8).

In recent years, a second generation of nonionic monomeric ratio 3.0 contrast media, *e.g.*, iopamidol and iohexol, and also an ionic ratio 3.0 medium, the monoacid dimeric ioxaglate, have become available for clinical trials. In contrast to metrizamide, these media tolerate autoclaving and can be supplied as sterile solutions, which is of great practical and economic importance.

The aim of the present investigation was to compare the effects on renal function and the adverse reactions of iohexol with those caused by the commonly used ionic ratio 1.5 medium metrizoate in renal angiography in humans.

The tolerance of iohexol in animal experimental models and in human volunteers has been similar to or better than that of metrizamide (9). Clinical trials in urography and angiography (1279 patients) have indicated a decreased number of adverse reactions compared with the ionic media (10).

MATERIALS AND METHODS

Study Design and Patients: Adult patients referred to the Department of Diagnostic Radiology, Malmö General Hospital, for renal angiography were eligible for the study. Patients with serum creatinine levels above 125 $\mu\text{mol/l}$ and patients who had received injection of contrast medium within 48 hours prior to angiography were excluded from the studies on renal function. Fifteen patients were examined with metrizoate and the subsequent 15 with iohexol. Age, body weight, and diagnosis are presented in TABLE I. The distribution of sex did not differ significantly between the groups. In the metrizoate group three patients were excluded from the renal function studies according to the exclusion criteria (two patients had an elevated level

¹ From the Department of Diagnostic Radiology, Malmö General Hospital, Malmö, Sweden. Received Feb. 15, 1983; accepted and revision requested April 15, 1983; revision received June 14, 1983.

This project was partly supported by a grant from the Swedish Medical Research Council (Project No. 3483).

TABLE I: Age, Body Weight, and Diagnosis

Contrast Medium	No. of Patients	Median Age & Range (yr)	Median Weight & Range (kg)	No. Patients with Carcinoma	No. Patients with Hypertension	No. Patients with Various* Diagnoses
Metrizoate	15	56 (25-72)	76 (44-102)	5	5	5
Iohexol	15	58 (22-74)	67 (49-89)	7	1	7

* Preoperative evaluation of hydronephrosis, calculi, pyelonephritis, and renal cysts.

of serum creatinine and one had undergone urography the day before renal angiography). Data from two other patients in the metrizoate group and from three patients in the iohexol group were incomplete. The number of patients included in the various statistical calculations is given in the tables.

Informed consent was obtained from each patient prior to entering the study.

Contrast Media: Pertinent data on the contrast media in the investigation are presented in TABLE II, where metrizamide also is listed for comparison. The chemical structures are shown in Figure 1. Total doses of contrast medium and doses selectively injected into the renal arteries are given in TABLE III. There were no significant differences in contrast medium doses between the groups with regard to the patients included in the analysis of serum creatinine.

Angiographic Procedure: The patients had fasted overnight and were premedicated with a suppository (diazepam, 10 mg). After local anesthesia, the angiography was started by femoral approach with a semiselective technique, using a polyethylene catheter (OD/ID 2.2/1.45 mm) shaped like a selective catheter, with an end hole for renal artery injection and six side holes for simultaneous aortic injection. Through this catheter, 30 ml of the contrast medium was injected with an automatic pressure injector (Medrad, Mark IV) (20 ml/s). Such an injection provides about 5 ml contrast medium through the end hole directly into the renal artery. In selective renal angiography,

using a catheter without side holes, 10-12 ml contrast medium was used (6-8 ml/s). When a renal carcinoma was found, 20-30 ml (8-10 ml/s) of the contrast medium was injected into the artery supplying the tumor.

Cr-51-EDTA Clearance: Clearance was determined the day before and the day after renal angiography by the single-injection technique according to Br  chner-Mortensen (11). The values were corrected for 1.73 m² of body surface.

Serum and Urine Analyses: Venous blood samples for analyses of serum albumin and serum creatinine were drawn the day before and the day after angiography. Urine samples were taken the day before, as soon as possible after angiography (0.5-4 hours), and the day after angiography for analyses of albumin and creatinine. Serum and urinary albumin levels were determined using the brom cresol-green method and electroimmunoassay method (12), respectively, whereas serum and urinary creatinine levels were determined using the Jaff   reaction. The urinary albumin concentration was expressed per gram of urinary creatinine, thereby relating albumin excretion to glomerular filtration rate.

Adverse Reactions: During and after the first contrast medium injection (semiselective), the patients were impartially observed for any spontaneous reactions, including comments or movements indicating discomfort. The patients were also questioned about any sensation of discomfort, and if present, whether the discomfort was mild, moderate, or severe. During the

angiographic procedure and 30 minutes after its termination, the patients were closely observed in the radiology department for any signs of adverse reactions. Observation was continued in the ward, where the patients were reinterviewed 24 hours after angiography.

Angiographic Quality: This was estimated by one observer, who was unaware of which contrast medium had been used.

Statistical Evaluation: Results were evaluated using the Wilcoxon test for paired observations or the Mann-Whitney U-test. Differences were considered significant when *p* values less than 0.05 were obtained.

RESULTS

The laboratory findings, except for serum albumin values, are given in TABLE IV.

Cr-51-EDTA Clearance and Serum Creatinine: There were no significant differences in preangiographic values of Cr-51-EDTA clearance and serum creatinine levels between the metrizoate and the iohexol group. There were no significant differences in postangiographic values of Cr-51-EDTA clearance compared with the preangiographic values in either group. In the metrizoate group the postangiographic serum creatinine levels were significantly higher than the preangiographic levels (*p* < 0.05). In the iohexol group there were no significant differences between pre- and postangiographic serum creatinine levels.

Albumin Concentration: There were no significant differences in preangiographic concentrations of urinary and serum albumin between the groups. In the metrizoate group there was a significant increase in urinary albumin values in the samples taken immediately after renal angiography (0.5-4 hours) (*p* < 0.01), but on the day after there were no significant differences compared with the preangiographic values. In the iohexol group there was no significant postangiographic increase in urinary albumin values. Finally, there were no significant differences between pre- and postangiographic serum albumin values in either group.

Adverse Reactions: In the metrizoate group all the patients but one reacted spontaneously to the contrast medium injection and three patients experienced the discomfort as severe. There was no spontaneous reaction in the iohexol group and no patient experienced the discomfort as severe. There were no other adverse reactions in either group.

Angiographic Quality: All the angi-

TABLE II: Pertinent Data on Contrast Media*

Generic Name	Trade Name	Iodine Content (mg/ml)	Osmolality (mol/kg H ₂ O)	Viscosity at 20° (mPa·s)
Metrizoate	Isopaque Cerebral	280	1.46	7.1
Iohexol	Omniopaque	300	0.69	11.6
Metrizamide†	Amipaque	280	0.43	9.7

* Data as given by the manufacturer.

† Metrizamide is included for comparison.

ographic studies were considered to be of good quality except for two in the metrizoate group. In both instances the patients were both obese and uncooperative.

DISCUSSION

Neither metrizoate nor iohexol affected the glomerular filtration rate (GFR) as measured by Cr-51-EDTA clearance on the day after angiography. Serum creatinine, which is also an expression of GFR, was not affected by renal angiography with iohexol; but in the metrizoate group there was a significant increase in serum creatinine level the day after angiography. Thus the results of the two methods estimating GFR were contradictory in the metrizoate group. Cr-51-EDTA clearance is a more reliable expression of GFR than serum creatinine level, and we conclude that there is no effect on GFR when measured the day after renal angiography with iohexol or metrizoate. The increased level of serum creatinine in the metrizoate group could be explained by a transient decrease in GFR in the immediate postangiographic period. The serum creatinine level depends on previous renal function; after a transient decrease in GFR, there is a time delay before the serum creatinine returns to the preangiographic level. Cr-51-EDTA clearance reflects glomerular filtration rate during the measuring period independent of previous function.

There are opposing views about contrast medium effects on GFR. Several authors have supported the use of high doses of contrast media for urography and angiography even in patients with renal insufficiency, as they did not observe any negative influence on GFR (13). Others have reported contrast-medium-induced decreases in GFR both in patients with healthy kidneys and in patients with renal failure (14-16). In our laboratory we have compared the effect of diatrizoate, metrizamide, and iohexol on GFR (measured by creatinine clearance) in high-dose renal angiography in dogs, and we have observed a GFR reduction to one-third of the preinjection level in

the immediate postangiographic period when diatrizoate was used, but metrizamide or iohexol had no effect on GFR (to be published).

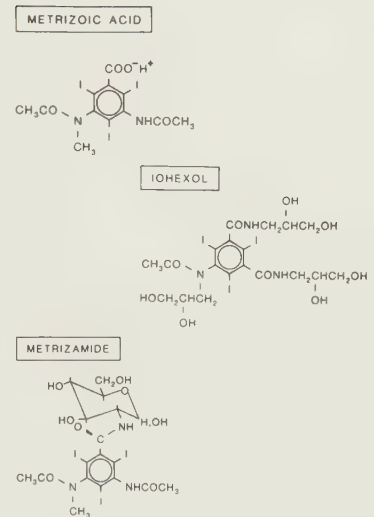
The present investigation demonstrated that iohexol did not induce any significant albuminuria in clinical renal angiography, whereas metrizoate induced a transient albuminuria. Transient albuminuria caused by an increased permeability of the glomerular membrane occurs frequently after renal angiography with metrizoate, diatrizoate, and metrizamide in both humans and dogs (4-6, 17). The albuminuria is related to the chemical structure of the contrast medium rather than to its osmolality (18).

The new generation of nonionic ratio 3.0 contrast media, such as iohexol and iopamidol, and also the ionic ratio 3.0 medium ioxaglate, cause significantly less albuminuria than diatrizoate in renal angiography in dogs (19). Ioxaglate did not induce albuminuria when used in clinical renal angiography (20).

The albuminuria is a sign of glomerular membrane dysfunction, but the significance of this phenomenon in contrast-medium-induced acute renal failure is not known. Disturbances in glomerular permeability, although transient, must be considered when discussing pathogenetic mechanisms, such as intratubular obstruction of precipitated material, and some reports suggest that this might be a major pathogenetic factor (21, 22).

In summary, iohexol did not induce any significant effects on renal function in clinical renal angiography, whereas metrizoate affected renal function, indicated both by a transient leakage of albumin and by laboratory findings consistent with a transient decrease in glomerular filtration rate. Although there were no statistical differences between the two groups with regard to the preangiographic values of Cr-51-EDTA clearance and serum creatinine level, one might suspect that the kidneys in the iohexol group were "healthier" than the kidneys in the metrizoate group, considering the median preangiographic values and that there were five patients

Figure 1



Chemical structures of metrizoate, iohexol, and metrizamide.

with hypertension in the metrizoate group and only one in the iohexol group. Therefore, two previous clinical trials in renal angiography, performed using the same technique and with metrizoate in the same concentration, have been reviewed in this respect (4, 17). The results are presented in TABLE V. According to these results one might conclude that the difference between metrizoate and iohexol, with regard to effects on renal function in the present investigation, is not related to minor differences in preangiographic kidney function between the two groups.

Contrast-medium-induced discomfort (sensations of heat and pain) is, of course, a disadvantage *per se*, but it might also cause motion unsharpness of the images. Since the introduction of metrizamide, several reports have stated that this discomfort was reduced when low-osmolar ratio 3.0 contrast media were used (2, 3, 20), and our results are in accordance with these reports.

TABLE III: Amount of Contrast Medium Used*

Contrast Medium	All Patients			Albuminuria Study		
	No. Patients	Median Selective† Dose & Range (ml)	Median Total Dose & Range (ml)	No. Patients	Median Selective† Dose & Range (ml)	Median Total Dose & Range (ml)
Metrizoate	15	25 (10-67)	165 (80-350)	10	28 (10-67)	168 (80-350)
Iohexol	15	30 (5-80)	165 (65-295)	14	30 (5-80)	168 (65-295)

There were no significant differences in contrast medium doses between the groups.

* Data on patients included in the analysis of albuminuria are given separately.

† Selective dose includes sum of doses to both kidneys.

TABLE IV: Laboratory Findings from the Present Study

Study	Contrast Medium	No. Patients	Preangiographic	Postangiographic	
			Day before (Median & Range)	1/2-4 hr After (Median & Range)	Day After (Median & Range)
Cr-51-EDTA clearance (ml/min)	Metrizoate	11	75 (35-129)	—	82 (46-137)
	Iohexol	15	94 (60-137)	—	93 (57-151)
Serum creatinine ($\mu\text{mol/l}$)	Metrizoate	11	114 (65-124)	—	119* (73-164)
	Iohexol	12	91 (69-125)	—	88 (71-124)
Urine albumin (g albumin/ g creatinine)	Metrizoate	10	0.043 (0.0072-0.18)	1.5† (0.014-22)	0.071 (0.0075-1.6)
		14	0.028 (0.0068-0.98)	0.050 (0.0060-0.62)	0.015 (0.0081-0.64)
	Iohexol	14			

* $p < 0.05$ compared with preangiographic value.† $p < 0.01$ compared with preangiographic value.

CONCLUSION

Iohexol did not affect glomerular filtration rate and glomerular permeability when used in renal angiography in humans. This might imply a reduced risk of contrast medium-induced acute renal failure.

Acknowledgments: We would like to thank Associate Professors Torsten Almén and Bertil Nosslin for valuable advice and discussions.

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TABLE V: Laboratory Findings from Two Previous Clinical Trials with Metrizoate in Renal Angiography*

Study	No. Patients	Preangiographic	Postangiographic	
		Day Before (Median & Range)	1/2-4 hr After (Median & Range)	Day After (Median & Range)
Serum creatinine ($\mu\text{mol/l}$)	22	87 (62-124)	—	97† (65-159)
	13	80 (62-88)	—	90† (65-124)
Urine albumin (g albumin/g creatinine)	22	0.037 (0.011-0.42)	1.1‡ (0.020-46)	0.074† (0.090-0.37)
	13	0.025 (0.011-0.10)	0.95‡ (0.22-46)	0.14‡ (0.024-0.37)

* From the two previous trials complete data were available on 22 patients with preangiographic serum creatinine levels below 125 $\mu\text{mol/l}$. A subgroup of 13 patients with preangiographic serum creatinine levels below 90 $\mu\text{mol/l}$ is also given.

† $p < 0.05$ compared with preangiographic values.‡ $p < 0.01$ compared with preangiographic values.



